

UNITED STATES DEPARTMENT OF COMMERCE  
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#10  
Pet. Denied

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
09/508,661	27-Nov-00	SACHETTO, ET AL	NONE

Title: XANTHUM GUM AND HPMC FOR THE TREATMENT  
OF IBD

Correspondence Address:

JAMES HELLWEGE

PMB 300

2101 CRYSTAL PLAZA ARCADE

ARLINGTON, VA 22202

Art Unit	Paper Number
----------	--------------

PATENT & TRADEMARK OFFICE

MAILED

NOV - 2 2001

LICENSING & REVIEW

Remailed  
01/04/02

Please find attached a communication from the Examiner regarding the  
Petition for Retroactive License under 37 CFR 5.25.



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231  
www.uspto.gov

#10  
Petition  
Denied

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/508,661	05/26/2000	JEAN-PIERRE SACHETTO		6789

2292 7590 01/04/2002  
BIRCH STEWART KOLASCH & BIRCH  
PO BOX 747  
FALLS CHURCH, VA 22040-0747

EXAMINER
----------

DEWITTY, ROBERT M

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 01/04/2002

#10

Please find below and/or attached an Office communication concerning this application or proceeding.



**UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office**

Address: COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

In re: Sachetto et al  
Serial No: 09/508,661  
Filed: May 26, 2000  
Docket: none

: DECISION ON REQUEST FOR  
: RETROACTIVE LICENSE UNDER  
: 37 CFR 5.25

PATENT & TRADEMARK OFFICE  
RECEIVED

Title: XANTHUM GUM AND HPMC FOR THE TREATMENT OF IBD

NOV - 2 2001

This is in response to the petition filed November 27, 2000 for a retroactive license.

LICENSING & REVIEW

37 CFR 5.25 requires the following:

- (1) A listing of each of the foreign countries in which the unlicensed patent application material was filed.
- (2) The dates on which the material was filed in each country,
- (3) A verified statement (oath or declaration) containing:
  - (i) An averment that the subject matter in question was not under a secrecy order at the time it was filed abroad, and that it is not currently under a secrecy order,
  - (ii) A showing that the license has been diligently sought after discovery of the proscribed foreign filing, and
  - (iii) An explanation of why the material was filed abroad through error and without deceptive intent without the required license under § 5.11 first having been obtained, and
- (4) The required fee ( § 1.17(h)).

The petition is Denied at this time in that the petition is defective in that the requirements set forth in 37 C.F.R. 5.25 (a)(3)(i-11) have not been satisfied.

Specifically, the petition does not include a statement that the subject matter in question was not under a secrecy order at the time of filing abroad, and that it is not currently under a secrecy order. Further, Mr. Buford declares that the proscribed foreign filing was discovered on or about September 25, 1998. However, the petition for retroactive license, on record, was not filed until November 27, 2000. The almost two year time span is not indicative of diligence sought. The petition for retroactive license does not provide a time line of what was done, when it was done and by whom, after discovery of the proscribed foreign filing.

Accordingly, the provisions of 37 CFR 5.25 having not been fully met, the petition is denied, and in the absence of any response within 60 days of the mailing date of this letter, such denial will be made final and the final action under 35 USC 185 will be taken. Extensions of time may be had under 37 C.F.R. 1.136(a).



Ian J. Lobo

Patent Examiner

Special Laws and Administration, Group 3600

(703) 306-4161

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Sachetto et al

Serial No. 09/508,661

Licensing and Review

Filed: May 26, 2000

For: XANTHUM GUM AND HPMC FOR THE  
TREATMENT OF IBD

**SECOND SUPPLEMENT TO PETITION FOR RETROACTIVE  
FOREIGN FILING LICENSE UNDER 37 CFR 5.25**

Honorable Commissioner of  
Patents and Trademarks  
Washington, D.C. 20231

Sir:

Supplemental to the Petitioner's submissions of December 30, 1999 and June 27, 2000 (copies attached), petitioner informs the Honorable Commissioner that the submission of December 30, 1999 incorrectly identified the above application as Serial No. 09/147,130 with a filing date of December 18, 1999. More correctly, the petition is directed to the subject matter of the above application having been assigned Serial No. 09/508,661. The instant application was filed on March 22, 2000, with the filing formalities subsequently being perfected on May 26, 2000.

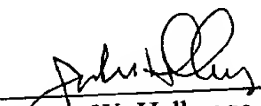
A foreign filing license has been granted for the above application. A copy of the filing receipt of the above application confirming the grant of the foreign filing license is attached.

Petitioner accordingly requests grant of a retroactive foreign filing license in accordance with the submissions of December 30, 1999 and June 27, 2000. As discussed in the attached declarations, petitioner requests issuance of a retroactive foreign filing license for the reason that the instant application is based on provisional UK applications that disclose and claim inventions based on contributions of three inventors, two of whom made their contributions to the respective inventions while residing in the United States. The two provisional UK applications ultimately formed the basis for PCT/GB98/02899, which is the priority application for the instant patent application. The failure to obtain a foreign filing license upon preparation of the provisional UK applications was inadvertent, through error, and without deceptive intent. The requested retroactive foreign filing license should accordingly be granted.

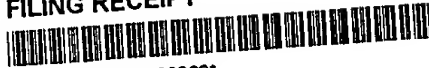
Please note the following new correspondence address for the undersigned attorney.

**James W. Hellwege**  
**PMB 300**  
**2101 Crystal Plaza Arcade**  
**Arlington, Virginia 22202**  
**Telephone: 571-212-1307**

Respectfully submitted,

BY:   
James W. Hellwege  
Registration No. 28,808

Filed: November 27, 2000

**FILING RECEIPT**

\*OC000000005168863\*

**UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office**Address: ASSISTANT SECRETARY AND  
COMMISSIONER OF PATENT AND TRADEMARKS  
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
09/508,661	05/26/2000	1614	1084	-	-	16	

JONES TULLAR & COOPER  
PO BOX 2266 EADS STATION  
ARLINGTON, VA 22202

Date Mailed: 06/09/2000

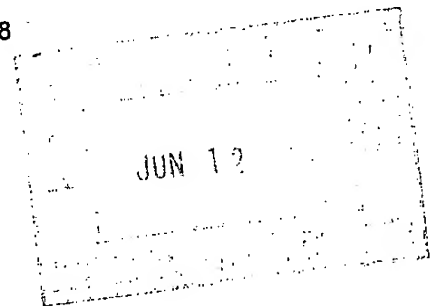
Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the PTO processes the reply to the Notice, the PTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

**Applicant(s)**JEAN-PIERRE SACHETTO, ARLESHEIM, SWITZERLAND;  
WILLIAM JEFFERY SANDBORN, MINNESOTA, MN;  
WILLIAM JOHN TREMAINE, MINNESOTA, MN;**Continuing Data as Claimed by Applicant**

THIS APPLICATION IS A 371 OF PCT/BG98/02899 09/25/1998

**Foreign Applications**UNITED KINGDOM 9720590.0 09/26/1997  
UNITED KINGDOM 9725346.2 11/28/1997

If Required, Foreign Filing License Granted 06/08/2000

**Title**PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF INFLAMMATORY BOWEL  
DISEASE**Preliminary Class**

514

6/8/00 2 28 PM

1. COMPANY 2. TITLE 3. INVENTOR 4. INVENTOR 5. INVENTOR 6. INVENTOR 7. INVENTOR 8. INVENTOR 9. INVENTOR 10. INVENTOR 11. INVENTOR 12. INVENTOR 13. INVENTOR 14. INVENTOR 15. INVENTOR 16. INVENTOR 17. INVENTOR 18. INVENTOR 19. INVENTOR 20. INVENTOR 21. INVENTOR 22. INVENTOR 23. INVENTOR 24. INVENTOR 25. INVENTOR 26. INVENTOR 27. INVENTOR 28. INVENTOR 29. INVENTOR 30. INVENTOR 31. INVENTOR 32. INVENTOR 33. INVENTOR 34. INVENTOR 35. INVENTOR 36. INVENTOR 37. INVENTOR 38. INVENTOR 39. INVENTOR 40. INVENTOR 41. INVENTOR 42. INVENTOR 43. INVENTOR 44. INVENTOR 45. INVENTOR 46. INVENTOR 47. INVENTOR 48. INVENTOR 49. INVENTOR 50. INVENTOR 51. INVENTOR 52. INVENTOR 53. INVENTOR 54. INVENTOR 55. INVENTOR 56. INVENTOR 57. INVENTOR 58. INVENTOR 59. INVENTOR 60. INVENTOR 61. INVENTOR 62. INVENTOR 63. INVENTOR 64. INVENTOR 65. INVENTOR 66. INVENTOR 67. INVENTOR 68. INVENTOR 69. INVENTOR 70. INVENTOR 71. INVENTOR 72. INVENTOR 73. INVENTOR 74. INVENTOR 75. INVENTOR 76. INVENTOR 77. INVENTOR 78. INVENTOR 79. INVENTOR 80. INVENTOR 81. INVENTOR 82. INVENTOR 83. INVENTOR 84. INVENTOR 85. INVENTOR 86. INVENTOR 87. INVENTOR 88. INVENTOR 89. INVENTOR 90. INVENTOR 91. INVENTOR 92. INVENTOR 93. INVENTOR 94. INVENTOR 95. INVENTOR 96. INVENTOR 97. INVENTOR 98. INVENTOR 99. INVENTOR 100. INVENTOR

**LICENSE FOR FOREIGN FILING UNDER  
Title 35, United States Code, Section 184  
Title 37, Code of Federal Regulations, 5.11 & 5.15**

**GRANTED**

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 36 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Office of Export Administration, Department of Commerce (15 CFR 370.10 (j)); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

**NOT GRANTED**

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

**PLEASE NOTE the following information about the Filing Receipt:**

- The articles such as "a," "an" and "the" are not included as the first words in the title of an application. They are considered to be unnecessary to the understanding of the title.
- The words "new," "improved," "improvements in" or "relating to" are not included as first words in the title of an application because a patent application, by nature, is a new idea or improvement.
- The title may be truncated if it consists of more than 600 characters (letters and spaces combined).
- The docket number allows a maximum of 25 characters.
- If your application was submitted under 37 CFR 1.10, your filing date should be the "date in" found on the Express Mail label. If there is a discrepancy, you should submit a request for a corrected Filing Receipt along with a copy of the Express Mail label showing the "date in."

Any corrections that may need to be done to your Filing Receipt should be directed to:

Assistant Commissioner for Patents  
Office of Initial Patent Examination  
Customer Service Center  
Washington, DC 20231

JONES, TULLAR, & COOPER, P.C.

Patent Office date stamp acknowledges receipt of paper below:

Application of:

Serial No. : *Sacchetto*

Filed :

Title : *Petition for Retroactive License*

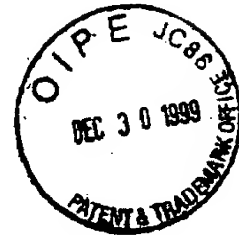
Title of Paper :

Date of Paper : *December 30, 1999*

Fee Payment :

Case No. : *\$130.00*

By :



JONES, TULLAR, & COOPER, P.C.

Patent Office date stamp acknowledges receipt of paper below:

Application of:

Serial No. :

Filed :

Title :

Title of Paper :

Date of Paper :

Fee Payment :

Case No. :

By :

*Supplement to Petition for  
Retroactive Foreign Filing  
License*



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

**SUPPLEMENT TO PETITION FOR RETROACTIVE  
FOREIGN FILING LICENSE UNDER 37 CFR 5.25**

Honorable Commissioner of  
Patents and Trademarks  
Washington, D.C. 20231

COPY

Sir:

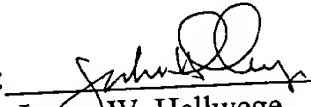
Petitioner filed a Petition for Retroactive Foreign Filing License on December 30, 1999. This petition has not yet been reviewed. A copy of the original petition is attached hereto..

Petitioner submits herewith Declarations of Anthony F. Burford and Watson McMunn in support of the original petition.

The petition fee was paid with the original filing.

Grant of this petition is respectfully requested.

Respectfully submitted,

BY:   
James W. Hellwege  
Registration No. 28,808

Jones, Tullar & Cooper, P.C.  
P.O. Box 2266 Eads Station  
Arlington, Virginia 22202  
703-415-1500  
Filed: June 27, 2000

**DECLARATION OF WATSON MCMUNN**  
**IN SUPPORT OF RETROACTIVE FILING LICENSE**

Honorable Commissioner of  
Patents and Trademarks  
Washington, D.C. 20231

COPY

Sir:

ATTENTION: LICENSING AND REVIEW

Sir:

I, Watson McMunn, do hereby state and declare as follows:

1. I prepared and filed U.K. provisional patent application Nos. 9720590.0 (filed September 26, 1997) and 9725346.2 (filed November 28, 1997). These provisional patent applications disclose and claim inventions based on contributions of three inventors, two of which (Drs. Sanborn and Tremaine) made their contributions while residing in the United States.

2. At the time of the preparation and filing of the above two U.K. patent applications I was employed by the London patent firm of W.H. Beck Greener & Co. I am no longer employed by the Beck Greener firm.

3. I was unaware at the time of the preparation of the above two U.K. provisional patent applications that foreign filing licenses should have been obtained from the U.S. Patent and Trademark Office. As a result, I did not obtain a foreign filing license prior to the preparation and filing of such patent applications. I only became aware of the necessity of obtaining a foreign filing license upon being contacted by my prior employer W.H. Beck Greener & Co. in connection with the execution of this declaration.

4. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any application or patent issuing therefrom to which this statement is directed.

Dated: 4/2/2000

Signed:   
Watson McMunn

**DECLARATION OF ANTHONY F. BURFORD IN  
IN SUPPORT OF RETROACTIVE FILING LICENSE**

Honorable Commissioner of  
Patents and Trademarks  
Washington, D.C. 20231

Sir:

ATTENTION: LICENSING AND REVIEW

COPY

Sir:

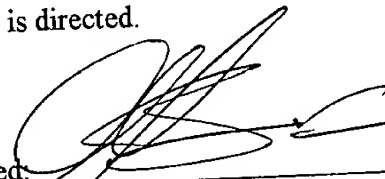
I, Anthony F. Burford, do hereby state and declare as follows:

1. I am Senior Partner of the patent firm of W.H. Beck Greener & Co in London, England.
2. I prepared and filed PCT application PCT/GB98/02899 on September 25, 1998. This PCT application claimed priority based on U.K. provisional patent application Nos. 9720590.0 (filed September 26, 1997) and 9725346.2 (filed November 28, 1997).
3. The noted U.K. provisional patent applications were prepared and filed by Watson McMunn of our firm. Mr. McMunn is no longer employed by W.H. Beck Greener & Co.
4. Shortly upon the filing of PCT application PCT/GB98/02899, I realized that foreign filing licenses should have been obtained from the U.S. Patent and Trademark Office prior to the preparation and filing of the noted U.K. provisional patent applications in view of the fact that the provisional patent applications disclose and claim inventions based on contributions of three inventors, two of which (Drs. Sanborn and Tremaine) made their contributions to the respective inventions while residing in the United States.

5. By letter of October 14, 1998 I informed Mr. James Hellwege of the patent firm of Jones, Tullar & Cooper, P.C. in Arlington, Virginia of the above facts and the need to obtain a foreign filing license. Mr. Hellwege was by that letter instructed to attend to the preparation of the necessary declarations for signature.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any application or patent issuing therefrom to which this statement is directed.

Dated: March 13, 2000

Signed:   
Anthony F. Burford

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

**PETITION FOR RETROACTIVE FOREIGN  
FILING LICENSE UNDER 37 CFR 5.25**

Honorable Commissioner of  
Patents and Trademarks  
Washington, D.C. 20231

COPY

Sir:

It is hereby requested that this petition for license for foreign filing the attached material be granted retroactively pursuant to 37 CFR 5.25.

No previous licenses have been granted nor sought in connection with this material.

With respect to the attached material for which a retroactive license is requested, the following applications have been filed abroad which contain the attached material, copies of which are attached:

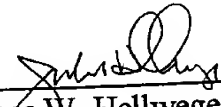
U.K. 9720590.0	filed September 26, 1997
U.K. 9725346.2	filed November 28, 1997
PCT/GB98/02899	filed September 25, 1998

A U.S. patent application corresponding to PCT/GB98/02899 was filed in the U.S. Patent and Trademark Office on December 18, 1998, and has been assigned Serial No. 09/147,130.

Verified statements which confirm that (1) the subject matter of the attached material was not under secrecy order at the time it was filed abroad, and that it is not currently under secrecy order, (2) the license is being diligently sought after discovery of the proscribed foreign filing, and (3) and that the foreign filing was undertaken without having first obtained a license through error and without deceptive intent will shortly follow.

The fee of \$130.00 for this petition is attached. Any deficiencies in fees may be charged to deposit account No. 10-1213.

Respectfully submitted,

BY:   
James W. Hellwege  
Registration No. 28,808

Jones, Tullar & Cooper, P.C.  
P.O. Box 2266 Eads Station  
Arlington, Virginia 22202  
415-1500  
Filed: December 30, 1999

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/715, 9/10</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/16454</b> <b>(43) International Publication Date:</b> 8 April 1999 (08.04.99)
<b>(21) International Application Number:</b> PCT/GB98/02899 <b>(22) International Filing Date:</b> 25 September 1998 (25.09.98) <b>(30) Priority Data:</b> 9720590.0 26 September 1997 (26.09.97) GB 9725346.2 28 November 1997 (28.11.97) GB <b>(71) Applicant (for all designated States except US):</b> MEDEVA EUROPE LIMITED [GB/GB]; 10 St. Jame's Street, London SW1A 1EF (GB). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> SACHETTO, Jean-Pierre [FR/CH]; Duchelweiher 13, CH-4051 Basel (CH). SAND- BORN, William, Jeffery [US/US]; 1132-7th Street, S.W., Rochester, MN 55902 (US). TREMAINE, William, John [US/US]; 625 Memorial Parkway, S.W., Rochester, MN 55905 (US). <b>(74) Agent:</b> BURFORD, Anthony, F.; W.H. Beck, Greener & Co., 7 Stone Buildings, Lincoln's Inn, London WC2A 3SZ (GB).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE <b>(57) Abstract</b>  A polysaccharide selected from xanthan gum and HPMC is used for the treatment or prophylaxis of IBD, especially Crohn's Disease, left-sided ulcerative colitis or pouchitis.		

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

PHARMACEUTICAL COMPOSITION FOR THE TREATMENT  
OF INFLAMMATORY BOWEL DISEASE

This invention relates to use of xanthan gum or  
5 hydroxypropylmethylcellulose (HPMC), particularly in the  
form of enemas for the treatment of inflammatory bowel  
disease (IBD), and to orally administrable and  
rectally/vaginally administrable compositions containing  
xanthan gum or HPMC as a therapeutically active agent.

10 Xanthan gum (CAS registry no. 1138-66-2) is described  
in USP NF XVI (p161) as a high molecular weight  
polysaccharide gum produced by a pure-culture fermentation  
of a carbohydrate with *Xanthomonas campestris*. It contains  
15 D-glucose and D-mannose as the dominant hexose units, along  
with D-glucuronic acid and is prepared as the sodium,  
potassium or calcium salt. It is widely used in  
pharmaceutical compositions as an emulsifying, stabilising  
and/or thickening agent.

20 HPMC (CAS registry no. 9004-65-3), otherwise known as  
hypromellose, is used as a suspending agent, tablet  
excipient, demulcent and/or viscosity increasing agent in  
pharmaceutical compositions. It is been used as a capsule  
25 or tablet coating, but the coating is soluble in gastric  
juices, and so would deliver the active in the capsule in  
the stomach.

IBD covers chronic non-specific inflammatory conditions  
30 of the gastro-intestinal tract, of which the two major forms  
are Crohn's disease and ulcerative colitis. The aetiology  
of these diseases is uncertain. Many inflammatory mediators  
have been proposed including prostanoids, leukotrienes,  
platelet activating factor, cytokines, and free oxygen  
35 radicals. Although specific inhibitors of most of these  
have been tried in experimental models, the most effective  
drugs currently available for these diseases have a broad  
activity against inflammatory processes.

Crohn's disease is characterised by thickened areas of the gastro-intestinal wall, with inflammation extending through all layers, deep ulceration and fissuring of the mucosa, and the presence of granulomas. Affected areas may occur in any part of the gastro-intestinal tract, although the terminal ileum is frequently involved, and they may be interspersed with areas of relatively normal tissue. Fistulas and abscesses may develop. Symptoms depend on the site of disease but may include abdominal pain, diarrhoea, fever, weight loss and rectal bleeding.

In ulcerative colitis, disease is continued to the colon and rectum. Inflammation is superficial but continuous over the affected area and granulomas are rare. In mild disease, the rectum alone may be affected (proctitis). In severe disease ulceration is extensive and much of the mucosa may be lost, with an increased risk of toxic dilatation of the colon, a potentially life-threatening complication.

Abdominal colectomy with mucosal proctectomy and ileal pouch-anal anastomosis is the preferred treatment for most patients with ulcerative colitis who require surgery. Pouchitis, the most common long-term complication of the procedure, occurs in up to 49% of patients at 10 years. Chronic pouchitis is distinguished from acute pouchitis by duration of symptoms for more than 4 weeks. The aetiology of pouchitis is unknown but it appears that both a history of ulcerative colitis and increased bacterial concentrations (relative to the normal ileum) are factors.

Currently, there is no satisfactory treatment for patients with chronic pouchitis who fail to respond to empiric antibiotic therapy. Although metronidazole is effective in some patients, long-term use is limited by concerns for neurotoxicity with peripheral neuropathy.

Numerous compounds have been examined in the last twenty years to find effective measures for the treatment of IBD. Such compounds include azathioprine, arsenicals, disodium cromoglycate, metronidazole, lignocaine, 5-aminosalicylic acid (5-ASA), fish oils, thalidomide and cyclosporin. The wide diversity of treatments, is an indication of the complexity and intransigence of IBD.

GB-A-1538123 (published 8th January 1979) disclosed the treatment of diverticulitis with a fibrous cellulosic material and a carboxylic polymer or salt which absorbs water and swells above pH 4. Specified carboxylic polymers include sodium carboxymethylcellulose (sodium CMC).

EP-A-0351987 (published 24th January 1990) disclosed the use of a polyacrylate, preferably a carbomer, for the treatment of IBD by oral or rectal administration.

US-A-4917890 (published 17th April 1990) disclosed the treatment of ulcerative colitis with a mucilaginous polysaccharide aloe extract.

WO-A-94/01436 (published 3rd March 1994; corresponding to US-A-5380522) disclosed treatment of irritable bowel syndrome (IBS) with an oral medicament of an anion-binding polymer and a hydrophilic polymer. Exemplified anion-binding polymers include xanthan gum.

WO-A-9407540 (published 14th April 1994; corresponding to EP-A-0620012 & US-A-5518711) disclosed an X-ray contrast medium containing 15-35 w/v% BaSO<sub>4</sub> and 0.15-0.6 w/v% xanthan gum dispersed in water. Lower xanthan gum concentrations are used with higher BaSO<sub>4</sub> concentrations. The medium is useful for double contrast enema examination of the large and the small intestine to detect inter alia Crohn's disease.

Sandborn et al (Gastroenterology 1994, 106, 1429-1435) reported a placebo-controlled trial of cyclosporin enemas in the treatment of mildly to moderately active left-sided ulcerative colitis. The vehicle for both the test and placebo enemas comprised 60 cm<sup>3</sup> water, 5 mg sorbitol (to make the vehicle isomolar) and 500 mg carboxymethylcellulose (CMC) (to suspend the hydrophobic cyclosporin). The placebo enema contained 3.5 cm<sup>3</sup> olive oil and use of this enema resulted in clinical improvement in nine out of twenty patients tested.

WO-A-9603115 (published 8th February 1996) disclosed aqueous foamable compositions having a delayed foaming action on expulsion from a pressurised container, comprising a water-immiscible liquefied gas, a water soluble polymer, and optionally, *inter alia*, a muco-adhesive agent. Exemplified water-soluble polymers include xanthan gum and HPMC and exemplified muco-adhesive agents include CMC. The compositions are of particular use for rectal or vaginal administration of pharmaceuticals to treat *inter alia* ulcerative colitis or Crohn's disease.

JP-A-08198757 (published 6th August 1996) discloses the use of high amylose starch, preferably administered with food materials, for the treatment of chronic ulcerative colitis.

The present Inventors found that xanthan gum and HPMC are effective *per se* for the treatment of IBD. This is surprising because, as indicated above, these materials are widely used in pharmaceutical compositions because of their assumed lack of pharmacological activity.

WO 98/01112 (published 15th January 1998; after the claimed priority dates of the present Application) discloses the treatment of distal IBD with a hydrogel formulation consisting essentially of a gelling agent and water with the optional presence of a pH-adjusting agent, plasticizer

and/or surfactant. The preferred gelling agents include HPMC and sodium CMC. The only specified distal IBD is ulcerative colitis.

5       According to a first aspect of the present invention, there is provided the use of a polysaccharide selected from xanthan gum and HPMC as a therapeutically active agent in the manufacture of a medicament for the treatment or prophylaxis of IBD.

10

By IBD we mean Crohn's Disease and ulcerative colitis including ulcerative proctitis, ulcerative proctosigmoiditis, lymphocytic colitis, intractable distal colitis, ileocolitis, collagenous colitis, microscopic colitis, pouchitis, radiation colitis, and antibiotic<sup>1</sup>-  
15 associated colitis. Xanthane gum and HPMC have been found to be particularly useful in the treatment of IBD conditions (such as pouchitis and left-sided ulcerative colitis) normally refractive to conventional therapy.

20

In a second aspect, the present invention provides a post-gastrically available delayed release oral (DRO) or rectally administrable pharmaceutical composition for the treatment or prophylaxis of IBD, said composition comprising  
25 a polysaccharide selected from xanthan gum and HPMC as a therapeutically active agent in an amount effective to treat IBD, together with a pharmaceutically acceptable carrier or vehicle. DRO compositions pass through the stomach substantially unaltered and deliver their active ingredient  
30 (which is within the tablet, capsule etc.) typically to the ileum up to and including the colon (i.e. where the diseased mucosa is).

According to a third aspect, the present invention  
35 provides a post-gastrically available DRO or rectally administrable pharmaceutical composition for the treatment or prophylaxis of IBD, said composition comprising a polysaccharide selected from xanthan gum and HPMC as the

sole therapeutically active agent together with a pharmaceutically acceptable carrier or vehicle.

5 In a fourth aspect, the present invention provides the use of a polysaccharide selected from xanthan gum and HPMC as the sole therapeutically active agent in the manufacture of a medicament for the treatment or prophylaxis of IBD.

10 In yet another aspect of the present invention, there is provided a method for the treatment or prophylaxis of IBD comprising contacting the diseased mucosa of the gastrointestinal tract with a therapeutic amount of a polysaccharide selected from xanthan gum and HPMC.

15 The polysaccharide can be used in the form of pharmaceutically acceptable salts of such as with alkali metals, usually sodium or potassium and alkaline earth metals, usually calcium or barium.

20 When the polysaccharide is present as the sole active agent, then no other therapeutically active agent such as 5-ASA or a corticosteroid will be present. Optionally, however, other therapeutic agents currently used or proposed for treating IBD can also be used sequentially in a  
25 different dosage form or concomitantly in the same dosage form as the polysaccharide. Examples of other such therapeutic agents are 5-ASA; immune modifiers such as azathioprine, cyclosporin and FK506; corticosteroids such as prednisolone, budesonide and hydrocortisone; antibiotics  
30 such as metronidazole, ciprofloxacin, amoxicillin, tetracycline and sulphamethoxazole; antidiarrheals such as loperamide and codeine sulphate; and local anaesthetics such as lignocaine.

35 The polysaccharide may be incorporated into a pharmaceutical composition to be administered either rectally, e.g. as an enema, or orally, for example, in coated tablets or capsules as described below. Also, the

polysaccharide may be formed into microgranules and coated, for example with Eudragit™ L or S and contained within a capsule similarly coated. In all solid compositions, it is preferable to include a disintegrant. Still further, the  
5 polysaccharide may be formulated in a number of dosage forms, e.g. uncoated or coated solid dosage forms for delayed release oral administration, for example using polymers in the Eudragit™ product range.

10 According to a preferred embodiment of the present invention, the pharmaceutical composition takes the form of an enema formulation such as a liquid or foam enema which is rectally administered to the lower colon. The enema  
15 formulations suitably comprise the polysaccharide dissolved or dispersed in a suitable flowable carrier vehicle, such as deionised and/or distilled water. The formulation can be thickened with one or more thickeners, can contain a buffer, and can also comprise an effective amount of a lubricant  
20 such as a natural or synthetic fat or oil, e.g. a tris-fatty acid glycerate or lecithin. Non-toxic non-ionic surfactants can also be included as wetting agents and dispersants. Unit doses of enema formulations can be administered from pre-filled bags or syringes. In the case of a pressurised  
25 enema formulation the carrier vehicle may also comprise an effective amount of a foaming agent such as n-butane, propane or i-butane, or the foaming agent/propellant could be held separately from the composition such as in a bag-in-bag or bag-in-can system as described in WO-A-9603115  
(incorporated herein by reference). Enema foams may also  
30 comprise expanding agents and foam-stabilisers.

The viscosity of the enema is preferably 10,000 to 70,000 mPa.s more preferably 10,000 to 70,000 mPa.s and most preferably 10,000 to 40,000 mPa.s. The pH is preferably 3.5  
35 to 7.5, especially 6.5 to 7.5.

A suitable dosage for xanthan gum in an enema or foam enema is 200 to 2000 mg, preferably 250 to 2000 mg, more

preferably 250 to 1650 mg, more preferably still 400 to 1650 mg, especially 550 to 1000 mg, in an aqueous or non-aqueous carrier. The volume of a liquid enema is typically 50 to 200 cm<sup>3</sup> preferably about 100 cm<sup>3</sup>. A suitable % w/w of  
5 xanthan gum in an enema is (based on 100 cm<sup>3</sup> enema) is 0.2% to 2% w/w, more preferably 0.3% to 2% w/w, more preferably still 0.4% to 2% w/w, more preferably still up to 1.65% w/w, and still more preferably 0.55% to 1%. Suitably the volume of a foam enema is 20 to 40 cm<sup>3</sup>. Based on the above  
10 preferred dosages, a suitable % w/w of xanthan gum in a foam enema (based on 40 cm<sup>3</sup> foam enema) is 1% to 4.25% w/w, more preferably 1.4% to 2.5%. A buffer is preferably added to the liquid or foam enema of xanthan gum to stabilise the pH. When a buffer is used it increases the viscosity and as a  
15 result, the maximum % w/w of xanthan gum that can be incorporated in the enema is about 1.7% w/w.

Typically the viscosity grade of xanthan gum used in a rectally administrable or DRO composition of the invention  
20 is 1,200 to 1,600 cP (mPa.s) at 1%.

Typically the viscosity grade of HPMC used in a rectally administrable or DRO composition of the invention is 3 to 100,000 cP (mPa.s). More particularly the grade of  
25 HPMC varies depending on the degree of hydroxypropoxy and methoxy substitution. Thus, preferably the degree of methoxy substitution is 15 to 30%, more preferably 19 to 30% such as 19 to 24% and 27 or 28 to 30%. The degree of hydroxypropoxy substitution is preferably 2 to 15%, more  
30 preferably 4 to 12%, such as 7 to 12% or 4 to 7.5%. The commercially available grades of HPMC include the following:

Product	% Methoxyl	% Hydroxypropoxyl	Viscosity cP (Mpa.s)	Relative Rate of Hydration
METHOCEL™ K Premium	19-24	7-12	3, 100, 4000, 15000, 100000	Fastest
METHOCEL™ E Premium	28-30	7-12	3, 5, 6, 15, 50, 4000	Next fastest
METHOCEL™ F Premium	27-30	4-7.5	50, 4000	Slower

The large range of viscosities allows a high dosage liquid enema or foam enema of HPMC to be formed by using a low viscosity grade of HPMC (i.e. a higher dosage than xanthan gum can be incorporated since the viscosity of the HPMC is less limiting). A suitable dosage of HPMC for a liquid enema or foam enema is 0.2 to 20 g, preferably 1 to 20g, more preferably 2 to 10 g, still more preferably 5 to 10 g for some IBD disease states and 1 to 5 g for other IBD disease states. A suitable % w/w of HPMC in a liquid enema or foam enema (based on 100 cm<sup>3</sup>) is 0.2% to 20% w/w, preferably 1% or 2% w/w to 20%, more preferably to an upper limit of 10% w/w, more preferably still 5% to 10%. A suitable % w/w of HPMC in a foam enema (at 40 cm<sup>3</sup>) is 1% to 50% w/w, more preferably 2.5% to 25% w/w, such as at least 7.5% w/w.

In a further embodiment of the invention, the polysaccharide is administered to the small intestine or colon of a patient by oral ingestion of a post-gastric delayed release (DRO) unit dosage form such as a tablet or capsule, comprising an effective amount of polysaccharide which is enterically coated so as to be released from the unit dosage form in the lower intestinal tract, e.g. in the

ileum and/or in the colon of the patient. Enteric coatings remain intact in the stomach, but dissolve and release the contents of the dosage form once it reaches the region where the pH is optimal for dissolution for the coating used.

5

A DRO formulation can also be achieved by coating a powder or microgranular formulation of the polysaccharide with coatings as mentioned above. The coated microgranules or material may then be compressed into tablets or packed into hard gelatin capsules suitable for oral administration. Suitable coatings and thicknesses to achieve this sustained release are disclosed in EP-A-0572486 (incorporated herein by reference).

15

The DRO form may optionally also be formulated to give a sustained release of the polysaccharide. The delayed release can be obtained, for example, by complexing the polysaccharide with a polyacrylic acid derivative (a polysaccharide polyacrylate complex) more particularly a polysaccharide carbomer complex. Alternatively particles of the polysaccharide complex could be incorporated into a hydrophobic matrix such as Gelucire™ (Gattefosse, France).

20

Aqueous film-coating technology is advantageously employed for the enteric coating of pharmaceutical dosage forms. A useful enteric coating is one that remains intact in the low pH of the stomach, but readily dissolves when the optimum dissolution pH of the particular coating is reached. This can vary between pH 3 to 7.5, preferably pH 5 to 7, most preferably pH 5.5 to 6.8, depending on the chemical composition of the enteric coating. The thickness of the coating will depend on the solubility characteristics of the coating material and the site to be treated.

30

35

By "delayed release" we mean that release is substantially post-gastrically and by "sustained release" we mean that the total release of the polysaccharide is slow

and sustained over a period of time, as opposed to being released as a bolus.

The majority of the release will be targeted to the part of the small intestine or colon where the active disease is prevalent and this varies for Crohn's disease and ulcerative colitis. Thus typically for an enteric coated capsule, the enteric coating should dissolve in the pH of the jejunum (about pH 5.5), ileum (about pH 6) or colon (about pH 6-7) so as to release the majority of the active from the jejunum to the colon - where most of the active disease is located in IBD. More particularly in the case of Crohn's disease most of the active disease is around the terminal ileum and so the enteric coating should dissolve about pH 5.5 to 6. In the case of ulcerative colitis, the disease is mostly in the colon and therefore the enteric coating should dissolve about pH 6 to 7, more particularly about pH 6.8.

Suitably the unit dosage of the polysaccharide in the delayed release oral composition is 200 to 2000 mg, preferably 250 to 2000 mg, more preferably 250 to 1650 mg, more preferably still 400 to 1650 mg, especially 550 to 1000 mg. A suitable % w/w of the polysaccharide in a DRO of the invention is 40 to 90% w/w, more preferably 60 to 80% w/w.

The above also is approximate to the total daily dosage and can be achieved by one or more unit dosages taken once, twice, three or more times daily. For example the total daily dosage is typically 200 to 6000 mg, preferably having an upper dosage limit of about 4000 mg and a lower limit of about 400 mg.

The DRO formulation can be provided as an enteric coated capsule containing the polysaccharide and having a coating thickness and dissolution profile as described in EP-A-0097651 (the contents of which are incorporated herein by reference). Suitable coating include cellulose acetate

phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose or polyvinyl acetate phthalate but the preferred coating material is an anionic polymer, especially one having the dissolution profile specified in EP-A-0097651, optionally in admixture with a neutral insoluble but permeable polymer. The presently preferred anionic polymers are anionic carboxylic polymers, i.e. polymers in which the anionic groups are at least predominantly free carboxylic and/or esterified carboxylic groups. It is particularly preferred that the anionic polymers should be acrylic polymers and the presently most preferred polymers are partly methyl esterified methacrylic acid polymers such as poly(methacrylic acid, methyl methacrylate) in which the ratio of free acid groups to ester groups is about 1:1 (e.g. those available from Röhm Pharma GmbH under the Trade Mark EUDRAGIT S). A neutral polymer coating, more specifically poly(ethylacrylate-methylmethacrylate) (e.g. Eudragit™ NE30D) may also be useful in some instances.

Examples of methacrylates (in the Eudragit™ range) for use as enteric coatings in accordance with the invention are as follows.

Chemical name	Trade name	CAS number
Poly(methacrylic acid, methyl methacrylate) 1:1	Eudragit™ L 100 Eudragit™ L 12.5 Eudragit™ L 12.5 P	[25806-15-1]
Poly(methacrylic acid, ethyl acrylate) 1:1	Eudragit™ L 30 D-55 Eudragit™ L 100-55	[25212-88-8]
Poly(methacrylic acid, methyl methacrylate) 1:2	Eudragit™ S 100 Eudragit™ S 12.5 Eudragit™ S 12.5 P	[25086-15-1]

In general coating thicknesses of about 25 to 200  $\mu\text{m}$ , and especially 75 to 150  $\mu\text{m}$ , are preferred using about 3 to 25 mg, preferably 8 to 15 mg of acidic coating material per

cm<sup>2</sup> of tablet or capsule surface. The precise coating thickness will however depend upon the solubility characteristics of the acidic material used and site to be treated.

5

In another preferred DRO or rectally administrable embodiment of the invention, sub 150µm particles of the polysaccharide or complex thereof (e.g. carbomer complex) is coated (partially or completely) or impregnated with a water insoluble anionic polymer. This prevents the formation of lumps and encourages the resulting hydrophobic particles of polysaccharide to disperse and coat the bowel wall when the contents of the DRO tablet or capsule are released. This technology is described in more detail in International Patent Application no. PCT/GB97/01847 (WO-A-9802573) (incorporated herein by reference).

By "sub 150µm particles", we mean such that 100% of particles in the DRO will pass through a 150 µm sieve. It is preferred that 100% of the hydrophillic carbomer particles pass a 100 µm sieve screen (i.e. they are sub 100 µm), more preferably at least 90%, especially at least 95%, of the hydrophilic particles pass a 63 µm sieve screen, more preferably a 50 µm sieve screen. The precise particle size must be small enough to provide a composition with a suitable degree of hydrophobicity following coating with the anionic polymer. Preferred particle size may vary according to the nature and amount of the cation present in the complex and the nature and amount of the anionic polymer.

30

The amount of anionic polymer used will depend upon the nature and amount of the cation present in the salt, the nature of the impregnating anionic polymer, and the degree of hydrophobicity required. A suitable amount can be determined by simple experimentation but usually the anionic polymer will be present in an amount of 10 to 50%, preferably 20 to 40, more preferably 25 to 35 and especially about one third, based on the weight of the carbomer

35

complex. Having regard to the small particle size, the amount of polymer will be less than the theoretical amount required to coat the particles, and the swelling and dissolution of the carbomer will not be controlled by pH.

5

The polysaccharide particles are impregnated/hydrophobised by milling and passing through a suitable sieve (as aforementioned), stirring the sieved particles into a mixture of e.g. isopropanol and water (solvent) and partly methyl esterified methacrylic acid polymer (e.g. Eudragit™ S100) at from 20 to 40% by weight of the polysaccharide particles (the solvent/coating solution having previously been agitated until clear), stirring and then evaporating the solvent under vacuum at about 50-70 °C to leave coated polysaccharide particles. Thereafter the resulting powder can be filled into gelatin capsules ready for enteric coating.

The invention will now be described by way of the following Examples.

Example 1 : Enema with HPMC.

947.6 g of purified water is preserved with 2 g of methyl and 0.4 g propyl parabens. 50 g (dry basis) of HPMC (Methocel E) low viscosity grade (50 cP/mPa.s) is dissolved under mechanical stirring at room temperature. The solution is degassed (air) under reduced pressure in an oven. A clear viscous enema is obtained having pH 6.9, viscosity (spindle 64, 1.5 rpm - 20°C on Brookfield DV 11): 4,000 mPa.s. The formation is packed in a bag-in-can canister or in an enema plastic pouch or in a PE bottle all having a 100 g enema capacity delivery, thus delivering a full dose of 5,000 mg HPMC.

Example 2 : Foam Enema Formulation with Xanthan Gum.

14,871 g of purified water containing 22 g of dissolved methyl paraben and 2 g of dissolved propyl paraben as  
5 preservatives were placed in a 20 litre Moltomat-Universal™  
MMU 20 homogenizer. Then 435g of xanthan gum (Keltrol™ TF)  
having a water content of 7.6% were dispersed in the  
preserved water under efficient homogenization and reduced  
pressure.

10

30 g of unbleached lecithin were then added and  
dispersed under homogenization and reduced pressure. At  
this stage the pH of the viscous gel obtained was 6.3. A  
solution then made of 0.45 g sodium hydroxide pellets and 20  
15 g of water was added and dispersed under reduced pressure.  
The pH then was 6.93. Finally 155 g of Polysorbate 80 (non-  
ionic surfactant) and 4 g of Citral (perfume) were added and  
dispersed under reduced pressure.

20

The final foam enema appeared as a slightly hazy gel,  
having a pH of 7.04 and a viscosity of 40,000 mPa.s at 20°C  
as measured using a Brookfield DV II viscometer (1.5 rpm,  
spindle 63).

25

A foam enema was then produced using this formulation  
by adding 2.2 g of n-butane per 100 g of the above  
formulation in a pressurised mixing unit and the mixture was  
then filled into bag-in-can aerosol canisters. Each  
canister contained 23 g of the mixture from which 21 g of  
30 foam was delivered through a valve and an applicator, i.e.  
about 530 mg of xanthan gum per delivered dose.

Example 3 : Liquid Enema Formulation with Xanthan Gum.

35

To 4,906 g of purified water containing 10 g of  
dissolved methyl paraben and 2 g of dissolved propyl paraben  
used as preservatives, 58.95 g of xanthan gum (Keltrol™ TF)  
containing 6.7% water (i.e. 55 g dry basis) was added in an

homogenizer and dispersed under efficient homogenization under reduced pressure. The pH of the gel obtained was 6.05 and the viscosity was 7,500 mPa.s (22°C, 1.5 rpm-spindle 63 Brookfield DV II). At this stage 23 g of sodium citrate. 5 2H<sub>2</sub>O was added as buffering agent. The pH went up to 7.15 and the viscosity was 40,000 mPa.s (measured as above). The formulation, which appears as a slightly hazy gel, was then packed into a bag-in-can canister equipped with a valve and an applicator and pressurised with nitrogen. If the bag of 10 the bag-in-can system is filled with 104 g of the formulation above then 100 g of the formulation can be delivered through the valve and applicator corresponding to a dose of 1.1 g of xanthan gum.

#### 15 Example 4 : Treatment of Chronic Pouchitis

The enema of Example 2 was given to twenty adult patients who had previously undergone total colectomy with mucosal proctectomy and ileal J-pouch anal anastomosis for 20 ulcerative colitis and who had active chronic pouchitis refractory to standard therapy. The patients had chronic pouchitis, as defined as continuous symptoms of pouchitis for more than 4 weeks and a Pouchitis Disease Activity Index (PDAI) score of at least 7 points on an 18 point scale. All 25 patients had either failed or were intolerant to metronidazole as well as other commonly used treatments for pouchitis. Mucosal inflammation, determined by endoscopic examination, was limited to the pouch and did not extend into the ileum proximal to the pouch.

30

The demographics of the patients entered into the study are presented in Table 1. There were no significant differences in the age, gender distribution, smoking history, time since the diagnosis of ulcerative colitis, 35 duration of pouch function, time since the first episode of pouchitis, duration of the current episode of pouchitis, or in the medications previously used for treatment of pouchitis. All patients had been on medication for

pouchitis, previously, and one half of the patients were on concurrent treatment for chronic pouchitis (Table 2).

5 Three patients had to discontinue treatment because of  
worsening of symptoms, but none developed dehydration or  
required hospitalization. Three patients had cramping  
discomfort in the pouch after taking the enema. One of the  
patients who developed cramps discontinued treatment because  
of the discomfort. One patient developed right lower  
10 abdominal pain and the study medication was discontinued.

The initial or final endoscopic or histologic scores of  
the patients are shown in Table 3.

TABLE 1

## PATIENT CHARACTERISTICS

Number of Patients	20
Age (mean)	40 (18-62)
Number of Men:Women	12:8
Number of Cigarette Smokers, current:former:never	1:2:17
Years since diagnosis of Ulcerative colitis. Median (range)	9 (3-32)
Months of pouch function. Median (range)	45 (4-161)
Months since the first episode of pouchitis. Median (range)	42 (3-151)
Months of current pouchitis episode. Median (range)	4 (0.8-151)

**TABLE 2****THERAPY FOR POUCHITIS (20 PATIENTS)**

Therapy	No. Of Patients	
	Current	Previous
<b>Antibiotics</b>		
Metronidazole	3	16
Ciprofloxacin	6	15
Amoxicillin/clavulanic acid	1	6
Tetracycline	0	3
Trimethoprine/sulfamethoxazole	1	0
<b>5-ASA</b>		
Sulfasalazine	1	5
Oral mesalamine	0	5
Mesalamine enemas	0	3
Mesalamine suppositories	0	3
<b>Corticosteroids</b>		
Prednisone	1	7
Hydrocortisone enemas	0	5
<b>Immune Modifiers</b>		
Azathioprine	0	0
Cyclosporine	0	0
FK506	0	0
<b>Antidiarrheals</b>		
Loperamide	5	3
Codeine sulfate	0	1

TABLE 3

DISEASE ACTIVITY AT BASELINE AND COMPLETION OF TREATMENT  
WITH XANTHAN GUM ENEMA

5

	Baseline Median (range)	Completion Median (range)
Clinical Score	4 (1,5)	3 (0,4) *
Endoscopy Score	5 (1,6)	4 (1,6)
Histology Score	2 (2,6)	# 2 (2,6) †
Total Score (PDAI)	11 (7,16)	9 (2,16) *

\*p<0.5 for within-group change. Baseline vs completion (signed rank test with two missing values at completion filled in by overall (groups) Baseline values).

10

In conclusion, six of the twenty patients discontinued therapy and nine of fourteen patients (64%) who completed the treatment improved (defined as a reduction in the PDAI score of 3 points or more). This is particularly surprising in view of the fact that the patients were refractory to conventional therapy.

15

CLAIMS

1. A post-gastrically available delayed release oral (DRO) or rectally administrable pharmaceutical composition for the treatment or prophylaxis of IBD, said composition comprising a polysaccharide selected from xanthan gum and HPMC as a therapeutically active agent in an amount effective to treat inflammatory bowel disease, together with a pharmaceutically acceptable carrier or vehicle.
2. A composition as claimed in Claim 1, wherein the polysaccharide is xanthan gum.
3. A composition as claimed in Claim 1, wherein the polysaccharide is HPMC.
4. A composition as claimed in any one of the preceding claims, wherein the polysaccharide is present as the sole therapeutically active ingredient.
5. A DRO composition as claimed in any one of the preceding claims.
6. A DRO composition as claimed in Claim 5 which is an enteric coated dosage form adapted to release its contents within the region of the jejunum to the colon.
7. A rectally administrable composition as claimed in any one of Claims 1 to 4.
8. A rectally administrable composition as claimed in Claim 7 which is a liquid enema or foam enema.
9. A liquid enema as claimed in Claim 8, wherein the polysaccharide is xanthan gum in a concentration of 0.4 to 2 % w/w.

10. A foam enema as claimed in Claim 8, wherein the polysaccharide is xanthan gum in a concentration of 1.4 to 2.5 w/w.
- 5 11. A liquid enema as claimed in Claim 8, wherein the polysaccharide is HPMC in a concentration of 1 to 20 % w/w.
12. A foam enema as claimed in Claim 8, wherein the polysaccharide is HPMC in a concentration of 2.5 to 25 %  
10 w/w.
13. A rectally administrable composition as claimed in Claim 7 or Claim 8, wherein the polysaccharide is xanthan gum in an amount of 400 to 2000 mg per unit dose.  
15
14. A rectally administrable composition as claimed in Claim 7 or Claim 8, wherein the polysaccharide is HPMC in an amount of 1 to 20 g per unit dose..
- 20 15. A DRO composition as claimed in Claim 5 or Claim 6, wherein the unit dose of the polysaccharide is 400 to 2000 mg.
16. The use of a polysaccharide selected from xanthan gum  
25 and HPMC as a therapeutically active agent in the manufacture of a medicament for the treatment or prophylaxis of IBD.
17. A use as claimed in Claim 16, wherein the  
30 polysaccharide is the sole therapeutically active agent in the medicament.
18. A use as claimed in Claim 16 or Claim 17 wherein the disease state is pouchitis.
- 35 19. A use as claimed in Claim 16 or Claim 17 wherein the disease state is left-sided ulcerative colitis.

20. A use as claimed in Claim 16 or Claim 17 wherein the disease state is Crohn's Disease.

21. A use as claimed in any one of Claims 16 to 20, wherein  
5 the medicament is a composition as defined in any one of Claims 1 to 15.

22. A method for the treatment or prophylaxis of IBD  
comprising contacting the diseased mucosa of the gastro-  
10 intestinal tract with a therapeutic amount of a polysaccharide selected from xanthan gum and HPMC.

PC

98/02899

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K31/715 A61K9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 04136 A (DAY CHARLES E) 3 March 1994 see page 7, line 21 - line 26	1, 2, 16, 18-21
X, P	WO 98 01112 A (JENSFELT BIRGITTA ; ASTRA AB (SE)) 15 January 1998 see page 2, line 10 - page 3, line 3 see page 4; example 1	1, 3-5, 7, 8, 11, 12, 14-22
X	WO 92 16214 A (NORWICH EATON PHARMA) 1 October 1992 see page 308 see page 33; example 14	1-3, 5-8
X	WO 91 01129 A (HENNING BERLIN GMBH) 7 February 1991 see page 8 - page 12; examples 1-3, 6 -/-	1, 3, 7, 8, 11, 12, 14

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

8 February 1999

Date of mailing of the international search report

18/02/1999

Name and mailing address of the ISA  
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 03115 A (SLAGEL DAVID ; SACHETTO JEAN PIERRE (CH)) 8 February 1996  see page 12 - page 13; example 1 ----	1,2,4, 7-10,13, 15
X	WO 96 30021 A (MAYO FOUNDATION) 3 October 1996 see page 4 - page 6; examples 1-3 ----	1,2,5-8, 13,15
X	EP 0 517 274 A (CEDONA PHARM BV) 9 December 1992 see page 3; example 1 ----	1,2,7-9, 13
X	FR 2 692 484 A (GOUCHET FRANCK) 24 December 1993 see page 3, line 15 - page 4, line 16 see page 5, line 21 - page 6, line 11 ----	1,3,5,6
X	WO 96 40078 A (CIBUS PHARMACEUTICAL INC) 19 December 1996 see page 42 - page 43; example 4 ----	1,3,5,15
X	CIFTCI K. ET AL: "Delivery of antitumor compounds to the rat colon: in vitro and in vivo evaluation" INT. J. PHARM., vol. 145, no. 1 2, 1996, pages 157-164, XP002092611 see page 158 - page 159 -----	1,3,5

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Office

## FILING RECEIPT

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02 December 1997

**PATENT APPLICATION NUMBER      9725346.2**

The Patent Office confirms receipt of a request for grant of a patent, details of which have been recorded as follows :

Filing Date (See Note)	: 28-NOV-97
Applicants	: MEDEVA EUROPE LIMITED
Description (No. of Sheets)	: 22
Claims (No. of Sheets)	: 3
Drawings (No. of Sheets)	: None
Abstract	: None
Statement of Inventorship (Form 7/77)	: None
Request for Search (Form 9/77)	: None
Request for Examination (Form 10/77)	: None
Priority Documents	: None
Translation of Priority Documents	: None
Divisional of Application	: None
Divisional Date Claimed	:
Other Attachments Received	: None

The application number included in the heading above should be quoted on all correspondence with The Patent Office.

Any queries on this receipt should be addressed to Mrs Lynne Payne, tel 01633 814570.

Note : The above filing date is provisional and may need to be amended if the provisions of section 15(1) of the Patents Act 1977 are not met.

# Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

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1. Your reference  
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2. Patent application number  
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3. Full name, address and postcode of the or of each applicant (underline all surnames)  
MEDEVA EUROPE LIMITED  
10 St. James's Street  
London SW1A 1EF

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation  
United Kingdom

4. Title of the invention  
PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

5. Name of your agent (if you have one)  
W.H. BECK, GREENER & CO.

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)  
W.H. BECK, GREENER & CO.  
7 Stone Buildings  
Lincoln's Inn  
London WC2A 3SZ

Patents ADP number (if you know it)  
323001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority application number (if you know it)	Date of filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

- a) any applicant named in part 3 is not an inventor, or
- b) there is an inventor who is not named as an applicant, or
- c) any named applicant is a corporate body.

Yes

PHARMACEUTICAL COMPOSITION FOR THE TREATMENT  
OF INFLAMMATORY BOWEL DISEASE

This invention relates to use of a polysaccharide gum  
5 such as Xanthan gum and hydroxypropylmethylcellulose (HPMC),  
particularly in the form of enemas for the treatment of  
inflammatory bowel disease (IBD), and to orally  
administrable and rectally/vaginally administrable  
compositions containing polysaccharide gum as a  
10 therapeutically active agent.

IBD covers chronic non-specific inflammatory conditions  
of the gastro-intestinal tract, of which the two major forms  
are Crohn's disease and ulcerative colitis. The aetiology  
15 of these diseases is uncertain. Many inflammatory mediators  
have been proposed including prostanoids, leukotrienes,  
platelet activating factor, cytokines, and free oxygen  
radicals. Although specific inhibitors of most of these  
have been tried in experimental models, the most effective  
20 drugs currently available for these diseases have a broad  
activity against inflammatory processes.

Crohn's disease is characterised by thickened areas of  
the gastro-intestinal wall, with inflammation extending  
25 through all layers, deep ulceration and fissuring of the  
mucosa, and the presence of granulomas. Affected areas may  
occur in any part of the gastro-intestinal tract, although  
the terminal ileum is frequently involved, and they may be  
interspersed with areas of relatively normal tissue.  
30 Fistulas and abscesses may develop. Symptoms depend on the  
site of disease but may include abdominal pain, diarrhoea,  
fever, weight loss and rectal bleeding.

In ulcerative colitis, disease is continued to the  
35 colon and rectum. Inflammation is superficial but  
continuous over the affected area and granulomas are rare.  
In mild disease, the rectum alone may be affected  
(proctitis). In severe disease ulceration is extensive and

much of the mucosa may be lost, with an increased risk of toxic dilatation of the colon, a potentially life-threatening complication.

5        Abdominal colectomy with mucosal proctectomy and ileal pouch-anal anastomosis is the preferred treatment for most patients with ulcerative colitis who require surgery. Pouchitis, the most common long-term complication of the procedure, occurs in up to 49% of patients at 10 years.

10      Chronic pouchitis is distinguished from acute pouchitis by duration of symptoms for more than 4 weeks. The aetiology of pouchitis is unknown but it appears that both a history of ulcerative colitis and increased bacterial concentrations (relative to the normal ileum) are factors.

15

         Currently, there is no satisfactory treatment for patients with chronic pouchitis who fail to respond to empiric antibiotic therapy. Although metronidazole is effective in some patients, long-term use is limited by

20      concerns for neurotoxicity with peripheral neuropathy.

         Numerous compounds have been examined in the last twenty years to find effective measures for the treatment of IBD. Such compounds include azathioprine, arsenicals,

25      disodium cromoglycate, metronidazole, lignocaine, 5-aminosalicylic acid (5-ASA), fish oils, thalidomide and cyclosporin. In EP-A-0351987, carbomer was proposed for treating IBD. The wide diversity of treatments, however, is an indication of the complexity and intransigence of this

30      condition.

         The inventors have now found that a polysaccharide (hydrogels/gums), in particular Xanthan gum and hydroxy propylmethyl cellulose (HPMC) and carboxymethylcellulose

35      (CMC) in therapeutic amounts is effective for the treatment of IBD.

This is surprising, since the polysaccharide gums/hydrogels such as Xanthan gum, CMC and HPMC with cellulosic a backbone are normally thought to be inert. On the other hand, high doses of the polysaccharides can be used with minimal side effects.

Although Xanthan gum and other polysaccharide gums have been present as a thickening agent in enemas used to treat IBD (for example, Xanthan gum in WO-A-9603115), it was never realised that they also had pharmacologically active properties for treatment of the disease. Furthermore in EP-A-620012 (US-A-5518711), Xanthan gum is used at 0.15-0.6 w/v% in a X-ray contrast medium administered to the colon to detect Crohn's disease. Again, however, there is no report of it also treating the disease.

In US-A-5380522 a medicament of an anion-binding polymer and a hydrophilic polymer was used to alleviate irritable bowel syndrome. Xanthan gum was one of a number of compounds mentioned under anion-binding polymer, but is was not used in the examples.

Accordingly in a first aspect of the invention there is provided the use of a polysaccharide (hydrogel/gum) as a therapeutically active agent in the preparation of a medicament for the treatment or prophylaxis of IBD.

In a second aspect of the invention, there is provided a post-gastrically available delayed release oral (DRO) or rectally administrable pharmaceutical composition comprising a polysaccharide gum as a therapeutically active agent in an amount of treat inflammatory bowel disease, together with a pharmaceutically acceptable carrier or vehicle.

In a third aspect of the invention there is provided a rectally administrable or post-gastrically available delayed release oral (DRO) pharmaceutical composition comprising a polysaccharide gum as the sole therapeutically active agent

together with a pharmaceutically acceptable carrier or vehicle.

5 In a fourth aspect of the invention there is provided the use of a polysaccharide gum as the sole therapeutically active agent in the manufacture of a medicament for the treatment or prophylaxis of IBD.

10 In yet another aspect of the invention there is provided a method for the treatment or prophylaxis of IBD comprising contacting the diseased mucosa of the gastrointestinal tract with therapeutic amounts of a polysaccharide gum.

15 Suitable polysaccharide gums for use in the invention are the naturally occurring high molecular weight polysaccharide gums and chemically modified derivatives thereof. Examples are as follows:

20 Xanthan gum, Sodium carboxymethyl cellulose, Tragacanth, Methylcellulose, Sodium alginate, Hydroxypropylmethylcellulose, (HPMC), Karya gum, Methylethylcellulose, Soluble starch, Pectin, Propylene glycol alginate, Hydroxy ethyl cellulose, Guar gum, Carra  
25 geenan, Agar gum, and Gum acacia (arabic).

Preferably the polysaccharide is water soluble, but in some aspects it may be adapted to be water-insoluble. In a preferred form of the invention, the polysaccharide is  
30 Xanthan gum HPMC and CMC.

Xanthan gum (CAS registry no. 1138-66-2) is monographed at USP NF XVI p161 and is described as a high molecular weight polysaccharide gum produced by a pure-culture  
35 fermentation of a carbohydrate with Xanthomonas campestris. It contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid and is prepared as the

sodium, potassium or calcium salt. Xanthan gum is commercially available from Systems Bio-Industries.

Another suitable polysaccharide gum is HPMC (CAS registry no. 9004-65-3), otherwise known as hypromellose. It is commercially available as Methocel® from The Dow Chemical Company. HPMC has been used as a coating for capsules, but the coating is soluble in gastric juices, and so would deliver the active in the capsule in the stomach. On the other hand, DRO compositions of the present invention pass through the stomach substantially unaltered and deliver their active ingredient (which is within the tablet, capsule etc.) typically to the ileum up to and including the colon (i.e. where the diseased mucosa is). HPMC has also been used as a swelling agent in tablets, but again the HPMC is not taught as therapeutically active for the treatment of IBD.

Carboxymethylcellulose (carmellose sodium) is a further suitable polysaccharide gum as shown by the examples hereinafter (CAS registry no. 9004-32-4).

Suitable pharmaceutically acceptable salts of the aforementioned polysaccharides are also within the scope of the invention and include alkali metals (e.g. sodium potassium) and alkaline earth metals (e.g. calcium or barium).

When a polysaccharide, such as Xanthan gum or HPMC is present as the sole active agent, then no other therapeutically active agent such as 5-ASA or corticosteroids would be present.

Optionally, however, other therapeutic agents currently used or proposed for treating IBD can also be used sequentially in a different dosage form or concomitantly in the same dosage form as the polysaccharide gum. Examples of other such therapeutic agents are 5-ASA, immune modifiers

such as azathioprine, cyclosporine and FK506, corticosteroids such as prednisolone, budesonide and hydrocortisone, antibiotics such as metronidazole, ciprofloxacin, amoxicillin, tetracycline and

5 sulphamethoxazole, and antidiarrheals such as loperamide and codeine sulphate, and local anaesthetics such as lignocaine.

By IBD we mean Crohn's Disease and ulcerative colitis including ulcerative proctitis, ulcerative

10 proctosigmoiditis, lymphocytic colitis, intractable distal colitis, ileocolitis, collagenous colitis, microscopic colitis, pouchitis, radiation colitis, and antibiotic-associated colitis. The invention has been found to be particularly useful in the treatment of IBD conditions (such

15 as pouchitis and left-sided ulcerative colitis) normally refractive to conventional therapy.

The polysaccharide may be incorporated into a pharmaceutical composition to be administered either

20 rectally, e.g. as an enema or foam enema, or orally, for example, in coated tablets or capsules as described below. Also, the polysaccharide may be formed into microgranules and coated, for example with Eudragit-L or S and contained within a capsule similarly coated. In all solid

25 compositions it is preferable to include a disintegrant. Still further, the polysaccharide may be formulated in a number of dosage forms, e.g. uncoated or coated solid dosage forms for non-delayed release or delayed release oral administration, for example using different polymers in the

30 Eudragit product range.

According to a preferred embodiment of the present invention, the pharmaceutical composition takes the form of an enema formulation such as a liquid or foam enema which is

35 rectally administered to the lower colon. The enema formulations would comprise a polysaccharide gum such as Xanthan gum dissolved or dispersed in a suitable flowable carrier vehicle, such as deionised and/or distilled water.

The formulation can be thickened with one or more thickeners, can contain a buffer, and can also comprise an effective amount of a lubricant such as a natural or synthetic fat or oil, e.g. a tris-fatty acid glycerate or lecithin. Non-toxic non-ionic surfactants can also be included as wetting agents and dispersants. Unit doses of enema formulations can be administered from pre-filled bags or syringes. In the case of a pressurised enema formulation the carrier vehicle may also comprise an effective amount of a foaming agent such as *n*-butane, propane or *i*-butane, or the foaming agent/propellant could be held separately from the composition such as in a bag-in-can system. Enema foams may also comprise expanding agents and foam-stabilisers.

The viscosity of the enema is preferably 10,000 to 70,000 mPa.s more preferably 10,000 to 70,000 mPa.S and most preferably 10,000 to 40,000 mPa.S. The pH is preferably 3.5 to 7.5, preferably 6.5 to 7.5.

A dosage for a polysaccharide such as Xanthan gum in an enema or foam enema is 200mg to 2000mg, more preferably at least about 250mg (or 300mg to 400mg) to 2000mg, more preferably 250mg to 1650mg, more preferably still 400mg to 1650mg, more preferably still 550 to 1000mg in an aqueous or non-aqueous carrier. The volume of the enema is typically 50ml to 200ml preferably about 100ml. A suitable % w/w of Xanthan gum in an enema is (based on 100ml enema) is 0.2% to 2% w/w, more preferably 0.3% to 2% w/w, more preferably still 0.4% to 2% w/w, more preferably still up to 1.65% w/w, and still more preferably 0.55% to 1% foam enema. The volume of a foam enema is 20ml to 40ml. Based on the above preferred dosages, a suitable % w/w of Xanthan gum in a foam enema (based on 40ml foam enema) is 1% to 4.25% w/w, more preferably 1.4% to 2.5%. A buffer is preferably added to the enema or foam enema of Xanthan gum to stabilise the pH. When a buffer is used it increases the viscosity and as a result, the maximum % w/w of Xanthan gum that can be incorporated in the enema/foam enema is about 1.7% w/w.

Typically the viscosity grade of Xanthan gum used in a rectally administrable or DRO composition of the invention is 1,200 to 1,600 cP at 1% and 1% KCl.

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Typically the viscosity grade of HPMC or CMC used in a rectally administrable or DRO composition of the invention is 3 to 100,000 CP. More particularly the grade of HPMC varies depending on the degree of hydroxypropoxy and methoxy substitution. Thus preferably the degree of methoxy substitution is 15 to 30%, more preferably 19 to 30% such as 19 to 24% and 27 or 28 to 30%. The degree of hydroxypropoxy substitution is preferably 2 to 15%, more preferably 4 to 12%, such as 7 to 12% or 4 to 7.5%. The commercially available grades of HPMC sold under the trade mark Methocel® are as follows.

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Product	% Methoxyl	% Hydroxypropoxyl	Viscosity cp	Relative Rate of Hydration
METHOCEL K Premium	19-24	7-12	3, 100, 4000, 15000, 100000	Fastest
METHOCEL E Premium	28-30	7-12	3, 5, 6, 15, 50, 4000	Next fastest
METHOCEL F Premium	27-30	4-7.5	50, 4000	Slower

The large range of viscosities allows a high dosage enema or foam enema of HPMC to be formed by using a low viscosity grade of HPMC (i.e. a higher dosage than Xanthan gum can be incorporated since the viscosity of the HPMC is less limiting). A suitable dosage of HPMC or CMC for a rectally administrable composition, such as an enema or foam enema is 0.2g to 20g, preferably at least 1g (or 2g) to 20g, more preferably still at least 1g to 10g, still more preferably 5g to 10g for some IBD disease states and at

20

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least 1g (or 2g) to 5g for other IBD disease states. A suitable % w/w of HPMC or CMC in an enema or foam enema (based on 100ml) is 0.2% to 20% w/w, more preferably 1% or 2% w/w to 20%, more preferably to an upper limit of 10% w/w, more preferably still 5% to 10%. A suitable % w/w of HPMC or CMC in a foam enema (at 40ml) is 1% to 50% w/w, more preferably 2.5% to 25% w/w, such as at least 7.5% w/w.

In a further embodiment of the invention, the polysaccharide gum is administered to the small intestine or colon of a patient by oral ingestion of a post-gastric delayed release (DRO) unit dosage form such as a tablet or capsule, comprising an effective amount of polysaccharide gum which is enterically coated so as to be released from the unit dosage form in the lower intestinal tract, e.g. in the ileum and/or in the colon of the patient. Enteric coatings remain intact in the stomach, but dissolve and release the contents of the dosage form once it reaches the region where the pH is optimal for dissolution for the coating used.

A DRO formulation can also be achieved by coating a powder or microgranular formulation of a polysaccharide gum of the invention with coatings as mentioned above. The coated microgranules or material may then be compressed into tablets or packed into hard gelatin capsules suitable for oral administration. Suitable coatings and thicknesses to achieve this sustained release are also disclosed in EP-A-0572486 (incorporated herein by reference).

30

The DRO form may optionally also be formulated to give a sustained release of the polysaccharide gum. The delayed release can be obtained, for example, by complexing the polysaccharide gum with a polyacrylic acid derivative (a gum-polyacrylate complex) more particularly a gum-carbomer complex. Alternatively particles of the gum or gum complex could be incorporated into a hydrophobic matrix such as Gelucire™ (Gattefosse, France).

35

Aqueous film-coating technology is advantageously employed for the enteric coating of pharmaceutical dosage forms. A useful enteric coating is one that remains intact in the low pH of the stomach, but readily dissolves when the optimum dissolution pH of the particular coating is reached. This can vary between pH 3 to 7.5, preferably pH 5 to 7, most preferably pH 5.5 to 6.8 depending on the chemical composition of the enteric coating. The thickness of the coating will depend on the solubility characteristics of the coating material and the site to be treated.

By delayed release we mean that release is substantially post-gastrically, and by sustained release we mean that the total release of the polysaccharide (e.g. Xanthan gum) is slow and sustained over a period of time, as opposed to being released as a bolus.

The majority of the release will be targeted to the part of the small intestine or colon where the active disease is prevalent and this varies for Crohn's disease and ulcerative colitis. Thus typically for an enteric coated capsule, the enteric coating should dissolve in the pH of the jejunum (about pH 5.5), ileum (about pH 6) or colon (about pH 6-7) so as to release the majority of the active from the jejunum to the colon - where most of the active disease is located in IBD. More particularly in the case of Crohn's disease most of the active disease is around the terminal ileum and so the enteric coating should dissolve about pH 5.5 to 6. In the case of ulcerative colitis, the disease is mostly in the colon and therefore the enteric coating should dissolve about pH 6 to 7, more particularly about pH 6.8.

Preferably the unit dosage of polysaccharide, such as HPMC, CMC or Xanthan gum in the delayed release oral composition is 200mg to 2000mg more preferably at least about 250mg (or 300mg to 400mg) to 2000mg, such as 250mg to 1650mg, more preferably 400mg to 1650mg, more preferably

still 550mg to 1000mg. A suitable % w/w of polysaccharide such as HPMC, CMC or Xanthan gum in a DRO of the invention is 40 to 90% w/w, more preferably 60 to 80% w/w.

5       The above also is approximate to the total daily dosage and can be achieved by one or more unit dosages taken once, twice, three or more times daily. For example the total daily dosage is typically 200mg to 6000mg, preferably having a upper dosage limit of about 4000mg and a lower limit of  
10       about 400mg.

      The DRO formulation can be provided in which an enteric coated capsule containing the polysaccharide gum has a coating , thickness of coating and dissolution profile  
15       described in EP-A-0097651 (the contents of which are incorporated herein by reference). Suitable coating include cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose or polyvinyl acetate phthalate but the preferred coating material is an anionic polymer,  
20       especially one having the dissolution profile specified in EP-A-0097651, optionally in admixture with a neutral insoluble but permeable polymer. The presently preferred anionic polymers are anionic carboxylic polymers, i.e. polymers in which the anionic groups are at least  
25       predominantly free carboxylic and/or esterified carboxylic groups. It is particularly preferred that the anionic polymers should be acrylic polymers and the presently most preferred polymers are partly methyl esterified methacrylic acid polymers such as poly(methacrylic acid, methyl  
30       methacrylate) in which the ratio of free acid groups to ester groups is about 1:1 ((e.g. those available from Röhm Pharma GmbH under the Trade Mark EUDRAGIT S). A neutral polymer coating, more specifically poly(ethylacrylate-methylmethacrylate) (e.g. Eudragit NE30D) may also be useful  
35       in some instances.

Examples of methacrylates (in the Eudragit range) for use as enteric coatings in accordance with the invention are as follows.

Chemical name	Trade name	CAS number
Poly(methacrylic acid, methyl methacrylate) 1:1	Eudragit L 100 Eudragit L 12.5 Eudragit L 12.5 P	[25806-15-1]
Poly(methacrylic acid, ethyl acrylate) 1:1	Eudragit L 30 D-55 Eudragit L 100-55	[25212-88-8]
Poly(methacrylic acid, methyl methacrylate) 1:2	Eudragit S 100 Eudragit S 12.5 Eudragit S 12.5 P	[25086-15-1]

5

In general coating thicknesses of about 25 to 200  $\mu\text{m}$ , and especially 75 to 150  $\mu\text{m}$ , are preferred using about 3 to 25 mg, preferably 8 to 15 mg of acidic coating material per  $\text{cm}^2$  of tablet or capsule surface. The precise coating thickness will however depend upon the solubility characteristics of the acidic material used and site to be treated.

10

In another preferred DRO or rectally administrable embodiment of the invention, sub 150 $\mu\text{m}$  particles of the polysaccharide gum or complex thereof (e.g. carbomer complex) is coated (partially or completely) or impregnated with a water insoluble anionic polymer. This prevents the formation of lumps and rather encourages the resulting hydrophobic particles of polysaccharide gum to disperse and coat the bowel wall when the contents of the DRO tablet or capsule are released. This technology is described in more detail in international application no. PCT/GB97/01847 (incorporated herein by reference).

20

25

By sub 150 $\mu\text{m}$  particles, we mean such that 100% of particles in the DRO will pass through a 150 $\mu\text{m}$  sieve. It is preferred that 100% of the hydrophillic carbomer particles pass a 100  $\mu\text{m}$  sieve screen (i.e. they are sub 100  $\mu\text{m}$ ), more preferably at least 90%, especially at least 95%, of the

30

hydrophilic particles pass a 63  $\mu\text{m}$  sieve screen, more preferably a 50  $\mu\text{m}$  sieve screen. The precise particle size must be small enough to provide a composition with a suitable degree of hydrophobicity following coating with the anionic polymer. Preferred particle size may vary according to the nature and amount of the cation present in the complex and the nature and amount of the anionic polymer.

The amount of anionic polymer used will depend upon the nature and amount of the cation present in the salt, the nature of the impregnating anionic polymer, and the degree of hydrophobicity required. A suitable amount can be determined by simple experimentation but usually the anionic polymer will be present in an amount of 10 to 50%, preferably 20 to 40, more preferably 25 to 35 and especially about one third, based on the weight of the carbomer complex. Having regard to the small particle size the amount of polymer will be less than the theoretical amount required to coat the particles, and the swelling and dissolution of the carbomer will not be controlled by pH.

The polysaccharide particles are impregnated/hydrophobised by milling and passing through a suitable sieve (as aforementioned), stirring the sieved particles into a mixture of e.g. isopropanol and water (solvent) and partly methyl esterified methacrylic acid polymer (e.g. Eudragit S100) at from 20 to 40% by weight of the polysaccharide particles (the solvent/coating solution having previously been agitated until clear), stirring then evaporating the solvent under vacuum at about 50-70° to leave coated polysaccharide particles. Thereafter the resulting powder can be filled into gelatin capsules ready for enteric coating.

The invention will now be described by way of the following examples.

**Example 1 : Enema with HPMC.**

947.6g of purified water is preserved with 2g of methyl  
5 and 0.4g propyl parabens. 50g (dry basis) of HPMC (Methocel  
E) low viscosity grade (50 cP) is dissolved under mechanical  
stirring at room temperature. The solution is degassed  
(air) under reduced pressure in an oven. A clear viscous  
enema is obtained pH : 6.9, viscosity (spindle 64, 1.5 rpm -  
10 20°C on Brookfield DV 11): 4'000 m.Pa.s. The formation is  
packed in a bag-in-can canister or in an enema plastic pouch  
or in a PE bottle all having a 100g enema capacity delivery,  
thus delivering a full dose of 5'000mg HPMC.

**Example 2 : Foam Enema Formulation with Xanthan gum.**

14,871g of purified water containing 22g of dissolved  
methyl paraben and 2g of dissolved propyl paraben as  
preservatives were placed in a 20 litre Moltomat-Universal  
20 MMU 20 homogenizer. Then 435g of Xanthan gum Keltrol TF  
having a water content of 7.6% (form the Company Kelco) were  
dispersed in the preserved water under efficient  
homogenization and reduced pressure.

25 30g of unbleached lecithin were then added and  
dispersed under homogenization and reduced pressure. At  
this stage the pH of the viscous gel obtained was 6.3. A  
solution then made of 0.45 g sodium hydroxide pellets and  
20g of water was added and dispersed under reduced pressure.  
30 The pH then was 6.93. Finally 155g of Polysorbate 80 (non-  
ionic surfactant) and 4g of Citral (perfume) were added and  
dispersed under reduced pressure.

The final foam enema appeared as a slightly hazy gel,  
35 having a pH of 7.04 and a viscosity of 40'000 mpa.s at 20°C  
as measured using a Brookfield DV II viscometer (1.5 rpm,  
spindle 63).

A foam enema was then produced using this formulation by adding 2.2g of n-butane per 100g of the above formulation in a pressurised mixing unit and the mixture was then filled into bag-in-can aerosol canisters. Each canister contained 23g of the mixture from which 21g of foam was delivered through a valve and an applicator, i.e. about 530 mg of Xanthan gum per delivered dose.

Liquid Enema Formulation : With Xanthan gum.

To 4,906g of purified water containing 10g of dissolved methyl paraben and 2g of dissolved propyl paraben used as preservatives, 58.95g of Xanthan gum Keltrol TF containing 6.7% water (i.e. 55g dry basis) was added in an homogenizer and dispersed under efficient homogenization under reduced pressure. The pH of the gel obtained was 6.05 and the viscosity was 7,500 mPa.s (22°C - 1.5 rpm-spindle 63 - Brookfield DV II). At this stage 23g of sodium citrate. 2H<sub>2</sub>O was added as buffering agent. The pH went up to 7.15 and the viscosity 40,000 mPa.s measured as above. The formulation, which appears as a slightly hazy gel, was then packed into a bag-in-can canister equipped with a valve and an applicator and pressurised with nitrogen. If the bag of the bag-in-can system is filled with 104g of the formulation above then 100g of the formulation can be delivered through the valve and applicator corresponding to a dose of 1.1g of Xanthan gum.

Example 3

The enema of Example 2 was then given to patients. The patients were twenty adults who had previously undergone total colectomy with mucosal proctectomy and ileal J-pouch anal anastomosis for ulcerative colitis and who had active chronic pouchitis refractory to standard therapy. Patients had chronic pouchitis, as defined as continuous symptoms of pouchitis for more than 4 weeks and a Pouchitis Disease Activity Index (PDAI) score of at least 7 points on an 18

point scale. All patients had either failed or were intolerant to metronidazole as well as other commonly used treatments for pouchitis. Mucosal inflammation, determined by endoscopic examination, was limited to the pouch and did not extend into the ileum proximal to the pouch.

The demographics of the patients entered into the study are presented in Table 1. There were no significant differences in the age, gender distribution, smoking history, time since the diagnosis of ulcerative colitis, duration of pouch function, time since the first episode of pouchitis, duration of the current episode of pouchitis, or in the medications previously used for treatment of pouchitis. All patients had been on medication for pouchitis, previously, and one half of the patients were on concurrent treatment for chronic pouchitis (Table 2).

TABLE 1

## PATIENT CHARACTERISTICS

5

Number of Patients	20
Age (mean)	40 (18-62)
Number of Men:Women	12:8
Number of Cigarette Smokers, current:former:never	1:2:17
Years since diagnosis of Ulcerative colitis. Median (range)	9 (3-32)
Months of pouch function. Median (range)	45 (4-161)
Months since the first episode of pouchitis. Median (range)	42 (3-151)
Months of current pouchitis episode. Median (range)	4 (.8-151)

**TABLE 2****THERAPY FOR POUCHITIS (20 PATIENTS)**

Therapy	No. Of Patients	
	Current	Previous
<b>Antibiotics</b>		
Metronidazole	3	16
Ciprofloxacin	6	15
Amoxicillin/clavulanic acid	1	6
Tetracycline	0	3
Trimethoprine/sulfamethoxazole	1	0
<b>5-ASA</b>		
Sulfasalazine	1	5
Oral mesalamine	0	5
Mesalamine enemas	0	3
Mesalamine suppositories	0	3
<b>Corticosteroids</b>		
Prednisone	1	7
Hydrocortisone enemas	0	5
<b>Immune Modifiers</b>		
Azathioprine	0	0
Cyclosporine	0	0
FK506	0	0
<b>Antidiarrheals</b>		
Loperamide	5	3
Codeine sulfate	0	1

TABLE 3

DISEASE ACTIVITY AT BASELINE AND COMPLETION OF TREATMENT  
WITH XANTHAN GUM ENEMA

	Baseline Median (range)	Completion Median (range)
Clinical Score	4 (1,5)	3 (0,4) *
Endoscopy Score	5 (1,6)	4 (1,6)
Histology Score	2 (2,6)	2 (2,6)
Total Score (PDAI)	11 (7,16)	9 (2,16) *

\*p<0.5 for within-group change. Baseline vs completion  
(signed rank test with two missing values at completion  
filled in by overall (groups) Baseline values).

Three patients had to discontinue treatment because of  
worsening of symptoms, but none developed dehydration or  
required hospitalization. Three patients had cramping  
discomfort in the pouch after taking the enema. One of the  
patients who developed cramps discontinued it because of the  
discomfort. One patient developed right lower abdominal  
pain and the study medication was discontinued.

The initial or final endoscopic or histologic scores of  
the patients are shown in Table 3.

In conclusion six of the twenty patients discontinued  
therapy and nine of fourteen patients (64%) who completed  
the treatment improved (defined as a reduction in the PDAI  
score of 3 points or more). This is particularly surprising

in view of the fact that the patients were refractory to conventional therapy.

Example 5; Liquid enema with CMC

5

An enema of carboxymethylcellulose (CMC) was made up with: 3.5ml olive oil in 12.5% alcohol, 60ml water, 5mg sorbitol and 500mg CMC (medium viscosity). The CMC was obtained from Spectrum Chemical Manufacturing Corp. Gardena, California, USA.

10

The CMC enema was given to 20 patients with left-side ulcerative colitis, which was chronically active and generally refractive to other drugs. The demographic data of the patients' is shown in Table 5 and their current and previous drug therapy is shown in Table 6. Treatment consisted of one enema nightly for 4 weeks. Only four patients were receiving concomitant oral corticosteroids and/or salicylates during the study. Enema treatment was discontinued in 3 of the 20 patients.

20

Table 5

	Placebo (n = 2)	
	Median	Range
Age at entry (yr)	43	21-69
Duration of ulcerative colitis (yr)	2	0-24
Duration of current symptoms (days)	225	14-6570
Extent of disease (cm)	38	10-60
Initial DAI score (range 0-12)	8	5-11
Initial HDAI score (range 0-4)	3	1-4
Sex (M/F)	10/10	

Table 6

	Placebo (n = 20) (%)
Current drug therapy	
No current treatment	20
Salicylates <sup>a</sup>	40
Steroids	15
Salicylates and steroids	25
Recently discontinued drug therapy <sup>b</sup>	
Topical steroids	30
Topical mesalamine	15
Previous drug therapy <sup>c</sup>	
Oral steroids	30
Topical steroids	45
Sulfasalazine	55
Olsalazine	10
Oral mesalamine	10
Topical mesalamine	40
Azathiophrine or 6-mercaptopurine	5

5   <sup>a</sup> - Salicylates are sulfasalazine, olsalazine, and oral mesalamine.

<sup>b</sup> - Therapy discontinued  $\leq 14$  days before study entry.

<sup>c</sup> - Therapy discontinued  $> 14$  days before study entry.

10       The response to the CMC enema of the invention is shown in Table 7.

Table 7

	Placebo	p*
	(n = 20)	
Disease activity Index		
Clinical remission	1	0.90
Clinical improvement <sup>b</sup>	9	0.90
Clinical failure	11	0.90
Histological disease activity Index	(n = 18)	
Histological remission	1	0.77
Histological improvement <sup>c</sup>	7	0.77
Histological failure	11	0.77

15       p\* - based on an extension of Fisher's Exact Test for ordered categories.

- <sup>b</sup> - Clinical improvement includes clinical remission.
- <sup>c</sup> - Histological improvement includes histological remission.

5           9 of 20 patients (45%) with left-sided ulcerative  
colitis who started the treatment, at 4 weeks showed  
clinical improvement. 9 of 17 (53%) patients who finished  
the treatment showed clinical improvement. This is a very  
significant result and is all the more surprising when one  
10 considers the refractory nature of the disease.

CLAIMS

1. A post-gastrically available delayed release oral (DRO) or rectally administrable pharmaceutical composition comprising a polysaccharide gum as a therapeutically active agent in an amount of treat inflammatory bowel disease, together with a pharmaceutically acceptable carrier or vehicle.
2. A DRO composition as claimed in Claim 1 wherein the dosage of the polysaccharide per unit dose is 200mg to 2000mg.
3. A DRO composition as claimed in Claim 2 wherein the dosage is 400mg to 2000mg.
4. A DRO composition as claimed in Claim 3 wherein the dosage is 550mg to 1000mg.
5. A DRO composition as claimed in any one of the preceding claims which is an enteric coated dosage form.
6. A DRO composition as claimed in Claim 5 wherein the enteric coating is adapted to release its contents anywhere from the jejunum to the colon.
7. A DRO composition as claimed in Claim 6 wherein the enteric coating is a partly methyl esterified methacrylic acid polymer or polyethylacrylate-methyl methacrylate.
8. A DRO composition as claimed in any one of the preceding claims wherein the dosage form is an enteric coated tablet or capsule or enteric coated microgranules.

9. A rectally administrable composition as claimed in Claim 1 which is an enema or foam enema.
- 5 10. A DRO or rectally administrable composition as claimed in any one of the preceding claims wherein the polysaccharide is present as the sole therapeutically active ingredient.
- 10 11. A DRO or rectally administrable composition as claimed in any one of the preceding claims wherein the polysaccharide is Xanthan gum.
- 15 12. A rectally administrable composition as claimed in Claim 11 wherein the dosage of the Xanthan gum is 0.2g to 2g.
- 20 13. A DRO or rectally administrable composition as claimed in Claim 12 wherein the dosage of the Xanthan gum is 0.4g to 2g.
- 25 14. A DRO or rectally administrable composition as claimed in any one of the preceding claims wherein the polysaccharide is HPMC or carboxymethylcellulose (CMC).
- 30 15. A rectally administrable composition as claimed in Claim 14 wherein the dosage of the HPMC or CMC is 0.2g to 20g.
- 35 16. A rectally administrable composition as claimed in Claim 15 wherein the dosage is 5g to 10g.
17. Use of polysaccharide gum in the preparation of a medicament for the treatment of inflammatory bowel disease.
18. Use as claimed in Claim 17 wherein the disease state is pouchitis.

19. Use as claimed in Claims 17 or 18 wherein the medicament is as claimed in any one of Claims 1 to 16.
- 5 20. The use of a polysaccharide gum as the sole therapeutically active agent in the manufacture of a medicament for the treatment or prophylaxis of inflammatory bowel disease.

ABSTRACT

PHARMACEUTICAL COMPOSITION FOR THE TREATMENT  
OF INFLAMMATORY BOWEL DISEASE

5

Polysaccharide gum in a post-gastrically delayed  
release oral (DRO) dosage form, or a rectally administrable  
10 form is used at 200 mg to 2000 mg for the treatment of  
inflammatory bowel disease.

Preferred polysaccharide gums are xantham gum,  
hydroxypropylmethylcellulose (HPMC) and carboxymethyl-  
15 cellulose (CMC). Also provided is DRO and rectally  
administrable compositions at 200 mg to 2000 mg dosage.



## FILING RECEIPT

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01633-814000

Your Ref. : WPM/P6982GB

14 November 1997

PATENT APPLICATION NUMBER      9720590.0

The Patent Office confirms receipt of a request for grant of a patent, details of which have been recorded as follows :

Filing Date (See Note)	: 26-SEP-97
Applicants	: MEDEVA EUROPE LIMITED
Description (No.of Sheets)	: 20
Claims (No.of Sheets)	: 2
Drawings (No.of Sheets)	: None
Abstract	: None
Statement of Inventorship (Form 7/77)	: None
Request for Search (Form 9/77)	: None
Request for Examination (Form 10/77)	: None
Priority Documents	: None
Translation of Priority Documents	: None
Divisional of Application	: None
Divisional Date Claimed	:
Other Attachments Received	: None

The application number included in the heading above should be quoted on all correspondence with The Patent Office.

Any queries on this receipt should be addressed to Mrs Lynne Payne. tel 01633 814570.

Note : The above filing date is provisional and may need to be amended if the provisions of section 15(1) of the Patents Act 1977 are not met.

**Request for grant of a patent**

*(see the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)*

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3. Full name, address and postcode of the or of each applicant <i>(underline all surnames)</i>	MEDEVA EUROPE LIMITED  10 St. James's Street London SW1A 1EF		
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If the applicant is a corporate body, give the country/state of its incorporation	United Kingdom		
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4. Title of the invention	PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE		
<hr/>			
5. Name of your agent <i>(if you have one)</i>	W.H. BECK, GREENER & CO.		
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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? <i>(Answer 'Yes' if:</i>	Yes		
a) any applicant named in part 3 is not an inventor, or			
b) there is an inventor who is not named as an applicant, or			
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PHARMACEUTICAL COMPOSITION FOR THE TREATMENT  
OF INFLAMMATORY BOWEL DISEASE

This invention relates to use of Xanthan gum,  
5 particularly in the form of enemas for the treatment of  
inflammatory bowel disease (IBD), and to orally  
administrable and rectally/vaginally administrable  
compositions containing Xanthan gum as the sole  
therapeutically active agent.

10

IBD covers chronic non-specific inflammatory conditions  
of the gastro-intestinal tract, of which the two major forms  
are Crohn's disease and ulcerative colitis. The aetiology  
of these diseases is uncertain. Many inflammatory mediators  
15 have been proposed including prostanoids, leukotrienes,  
platelet activating factor, cytokines, and free oxygen  
radicals. Although specific inhibitors of most of these  
have been tried in experimental models, the most effective  
drugs currently available for these diseases have a broad  
20 activity against inflammatory processes.

Crohn's disease is characterised by thickened areas of  
the gastro-intestinal wall, with inflammation extending  
through all layers, deep ulceration and fissuring of the  
25 mucosa, and the presence of granulomas. Affected areas may  
occur in any part of the gastro-intestinal tract, although  
the terminal ileum is frequently involved, and they may be  
interspersed with areas of relatively normal tissue.  
Fistulas and abscesses may develop. Symptoms depend on the

site of disease but may include abdominal pain, diarrhoea, fever, weight loss and rectal bleeding.

In ulcerative colitis, disease is continued to the  
5 colon and rectum. Inflammation is superficial but  
continuous over the affected area and granulomas are rare.  
In mild disease, the rectum alone may be affected  
(proctitis). In severe disease ulceration is extensive and  
much of the mucosa may be lost, with an increased risk of  
10 toxic dilatation of the colon, a potentially life-  
threatening complication.

Abdominal colectomy with mucosal proctectomy and ileal  
pouch-anal anastomosis is the preferred treatment for most  
15 patients with ulcerative colitis who require surgery.  
Pouchitis, the most common long-term complication of the  
procedure, occurs in up to 49% of patients at 10 years.  
Chronic pouchitis is distinguished from acute pouchitis by  
duration of symptoms for more than 4 weeks. The aetiology  
20 of pouchitis is unknown but it appears that both a history  
of ulcerative colitis and increased bacterial concentrations  
(relative to the normal ileum) are factors.

Currently, there is no satisfactory treatment for  
25 patients with chronic pouchitis who fail to respond to  
empiric antibiotic therapy. Although metronidazole is  
effective in some patients, long-term use is limited by  
concerns for neurotoxicity with peripheral neuropathy.

Numerous compounds have been examined in the last twenty years to find effective measures for the treatment of IBD. Such compounds include azathioprine, arsenicals, disodium cromoglycate, metronidazole, lignocaine, 5-aminosalicylic acid (5-ASA), fish oils, thalidomide and cyclosporin. In EP-A-0351987, carbomer was proposed for treating IBD. The wide diversity of treatments, however, is an indication of the complexity and intransigence of this condition.

10

The inventors have now found that a polysaccharide (hydrogels/gums), in particular Xanthan gum in therapeutic amounts is effective for the treatment of IBD.

15 This is surprising, since the polysaccharide gums/hydrogels such as Xanthan gum with its cellulosic backbone are normally thought to be inert. On the other hand, high doses of the polysaccharides can be used with minimal side effects.

20

Although Xanthan gum and other polysaccharide gums have been present as a thickening agent in enemas used to treat IBD (for example, Xanthan gum in WO-A-9603115), it was never realised that they also had pharmacologically active properties for treatment of the disease. Furthermore in EP-A-620012 (US-A-5518711), Xanthan gum is used at 0.15-0.6 w/v% in a X-ray contrast medium administered to the colon to detect Crohn's disease. Again, however, there is no report of it also treating the disease.

In US-A-5380522 a medicament of an anion-binding polymer and a hydrophilic polymer was used to alleviate irritable bowel syndrome. Xanthan gum was one of a number  
5 of compounds mentioned under anion-binding polymer, but is was not used in the examples.

Accordingly in a first aspect of the invention there is provided the use of a polysaccharide (hydrogel/gum) as a  
10 therapeutically active agent in the preparation of a medicament for the treatment or prophylaxis of IBD.

In a second aspect of the invention there is provided a rectally or post-gastrically delayed release oral (DRO)  
15 administrable pharmaceutical composition comprising a polysaccharide gum as the sole therapeutically active agent together with a pharmaceutically acceptable carrier or vehicle.

20 In a third aspect of the invention there is provided the use of a polysaccharide gum as the sole therapeutically active agent in the manufacture of a medicament for the treatment or prophylaxis of IBD.

25 In yet another aspect of the invention there is provided a method for the treatment or prophylaxis of IBD comprising contacting the diseased mucosa of the gastrointestinal tract with a polysaccharide gum.

Suitable polysaccharide gums for use in the invention are the naturally occurring high molecular weight polysaccharide gums and chemically modified derivatives thereof. Examples are as follows:

- 5
- Xanthan gum, Sodium carboxymethyl cellulose, Tragacanth, Methylcellulose, Sodium alginate, Hydroxypropylmethylcellulose, Karyn gum, Methylethylcellulose, Soluble starch, Pectin, Propylene glycol alginate, Hydroxy ethyl cellulose, Guar gum, Carra
- 10 geenan, Agar gum, and Gum acacia (arabic).

- Preferably the polysaccharide is water soluble. In a preferred form of the invention, the polysaccharide is
- 15 Xanthan gum.

- Xanthan gum (CAS registry no. 1138-66-2) is monographed at USP NF XVI p161 and is described as a high molecular weight polysaccharide gum produced by a pure-culture
- 20 fermentation of a carbohydrate with *Xanthomonas campestris*. It contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid and is prepared as the sodium, potassium or calcium salt.

- 25 Suitable pharmaceutically acceptable salts of the aforementioned polysaccharides are also within the scope of the invention and include alkali metals (e.g. sodium potassium) and alkaline earth metals (e.g. calcium or barium).

When a polysaccharide, such as Xanthan gum is present as the sole active agent, then no other therapeutically active agent such as 5-ASA or corticosteroids would be present.

Optionally, however, other therapeutic agents currently used or proposed for treating IBD can also be used sequentially in a different dosage form or concomitantly in the same dosage form as the polysaccharide gum. Examples of other such therapeutic agents are 5-ASA, immune modifiers such as azathioprine, cyclosporine and FK506, corticosteroids such as prednisolone, budesonide and hydrocortisone, antibiotics such as metronidazole, ciprofloxacin, amoxicillin, tetracycline and sulphamethoxazole, and antidiarrheals such as loperamide and codeine sulphate, and local anaesthetics such as lignocaine.

By IBD we mean Crohn's Disease and ulcerative colitis including ulcerative proctitis, ulcerative proctosigmoiditis, lymphocytic colitis, intractable distal colitis, ileocolitis, collagenous colitis, microscopic colitis, pouchitis, radiation colitis, and antibiotic-associated colitis. The invention has been found to be particularly useful in the treatment of pouchitis.

The polysaccharide may be incorporated into a pharmaceutical composition to be administered either or rectally, e.g. as an enema or foam enema, or orally, for

example, in coated tablets or capsules as described below. Also, the polysaccharide may be formed into microgranules and coated, for example with Eudragit-L or S and contained within a capsule similarly coated. In all solid  
5 compositions it is preferable to include a disintegrant. Still further, the polysaccharide may be formulated in a number of dosage forms, e.g. uncoated or coated solid dosage forms for non-delayed release or delayed release oral administration, for example using different polymers in the  
10 Eudragit product range.

According to a preferred embodiment of the present invention, the pharmaceutical composition takes the form of an enema formulation such as a liquid or foam enema which is  
15 vaginally or rectally administered to the lower colon. The enema formulations would comprise a polysaccharide gum such as Xanthan gum dissolved or dispersed in a suitable flowable carrier vehicle, such as deionised and/or distilled water. The formulation can be thickened with one or more  
20 thickeners, can contain a buffer, and can also comprise an effective amount of a lubricant such as a natural or synthetic fat or oil, e.g. a tris-fatty acid glycerate or lecithin. Non-toxic non-ionic surfactants can also be included as wetting agents and dispersants. Unit doses of  
25 enema formulations can be administered from pre-filled bags or syringes. In the case of a pressurised enema formulation the carrier vehicle may also comprise an effective amount of a foaming agent such as n-butane, propane or i-butane, or the foaming agent could be held separately from the

composition such as in a bag-in-can system. Enema foams may also comprise expanding agents and foam-stabilisers.

The viscosity of the enema is preferably 10,000 to 70,000 mPa.s more preferably 10,000 to 70,000 mPa.S and most preferably 10,000 to 40,000 mPa.S. The pH is preferably 3.5 to 7.5, preferably 6.5 to 7.5.

A preferred dosage for an enema is 200mg to 2000mg, more preferably 250mg to 1650mg, more preferably still 550 to 1000mg in an aqueous or non-aqueous carrier. The volume of the enema is typically 50ml to 200ml preferably about 100ml.

In a further embodiment of the invention, the polysaccharide gum is administered to the small intestine or colon of a patient by oral ingestion of a post-gastric delayed release (DRO) unit dosage form such as a tablet or capsule, comprising an effective amount of polysaccharide gum which is enterically coated so as to be released from the unit dosage form in the lower intestinal tract, e.g. in the ileum and/or in the colon of the patient. Enteric coatings remain intact in the stomach, but dissolve and release the contents of the dosage form once it reaches the region where the pH is optimal for dissolution for the coating used.

The DRO form may optionally also be formulated to give a sustained release of the polysaccharide gum. The delay

release can be obtained, for example, by complexing the polysaccharide gum with a polyacrylic acid derivative (a gum-polyacrylate complex) more particularly a gum-carbomer complex. Alternatively particles of the gum or gum complex  
5 could be incorporated into a hydrophobic matrix such as Gelucire™ (Gattefosse, France).

Aqueous film-coating technology is advantageously employed for the enteric coating of pharmaceutical dosage  
10 forms. A useful enteric coating is one that remains intact in the low pH of the stomach, but readily dissolves when the optimum dissolution pH of the particular coating is reached. This can vary between pH 3 to 7.5 depending on the chemical composition of the enteric coating. The thickness of the  
15 coating will depend on the solubility characteristics of the coating material and the site to be treated.

By delayed release we mean that release is substantially post-gastrically, and by sustained release we  
20 mean that the total release of the Xanthan gum is slow and sustained over a period of time, as opposed to being released as a bolus.

The majority of the release will be targeted to the  
25 part of the small intestine or colon where the active disease is prevalent and this varies for Crohn's disease and ulcerative colitis. Thus typically for an enteric coated capsule, the enteric coating should dissolve in the pH of the jejunum, ileum or colon.

Preferably the unit dosage of Xanthan gum in the delayed release oral composition is 200mg to 2000mg more preferably about 250mg to 1650mg, more preferably still  
5 550mg to 1000mg.

The above also is approximate to the total daily dosage and can be achieved by one or more unit dosages taken once, twice, three or more times daily.

10

The DRO formulation can be provided in which an enteric coated capsule containing the polysaccharide gum has a coating, thickness of coating and dissolution profile described in EP-A-0097651 (the contents of which are  
15 incorporated herein by reference). Suitable coating include cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose or polyvinyl acetate phthalate but the preferred coating material is an anionic polymer, especially one having the dissolution profile specified in  
20 EP-A-0097651, optionally in admixture with a neutral insoluble but permeable polymer. The presently preferred anionic polymers are anionic carboxylic polymers, i.e. polymers in which the anionic groups are at least predominantly free carboxylic and/or esterified carboxylic  
25 groups. It is particularly preferred that the anion polymers should be acrylic polymers and the presently most preferred polymers are partly methyl esterified methacrylic acid polymers in which the ratio of free acid groups to ester groups is about 1:1 (i.e. Eudragit L), especially,

about 1:2 (i.e. Eudragit S), or a neutral polymer coating, more specifically poly(ethylacrylate-methylmethacrylate) (e.g. Eudragit NE30D).

5        A DRO formulation can also be achieved by coating a powder or microgranular formulation of a polysaccharide gum of the invention with coatings as mentioned above. The coated microgranules or material may then be compressed into tablets or packed into hard gelatin capsules suitable for  
10 oral administration. Suitable coatings and thicknesses to achieve this sustained release are also disclosed in EP-A-0572486 (incorporated herein by reference).

In general coating thicknesses of about 25 to 200  $\mu\text{m}$ ,  
15 and especially 75 to 150  $\mu\text{m}$ , are preferred using about 3 to 25 mg, preferably 8 to 15 mg of acidic coating material per  $\text{cm}^2$  of tablet or capsule surface. The precise coating thickness will however depend upon the solubility characteristics of the acidic material used and site to be  
20 treated.

In another preferred DRO or rectally administrable embodiment of the invention, sub 150 $\mu\text{m}$  particles of the polysaccharide gum or complex thereof (e.g. carbomer  
25 complex) is coated (partially or completely) or impregnated with a water insoluble anionic polymer. This prevents the formation of lumps and rather encourages the resulting hydrophobic particles of polysaccharide gum to disperse and coat the bowel wall when the contents of the DRO tablet or

capsule are released. This technology is described in more detail in international application no. PCT/GB97/01847 (incorporated herein by reference).

5 By sub 150µm particles, we mean such that 100% of particles in the DRO will pass through a 150µm sieve. It is preferred that 100% of the hydrophilic carbomer particles pass a 100 µm sieve screen (i.e. they are sub 100 µm), more preferably at least 90%, especially at least 95%, of the  
10 hydrophilic particles pass a 63 µm sieve screen, more preferably a 50 µm sieve screen. The precise particle size must be small enough to provide a composition with a suitable degree of hydrophobicity following coating with the anionic polymer. Preferred particle size may vary according  
15 to the nature and amount of the cation present in the complex and the nature and amount of the anionic polymer.

The presently preferred anionic polymers are anionic carboxylic polymers, i.e. polymers in which the anionic  
20 groups are at least predominantly free carboxylic and/or esterified carboxylic groups. It is particularly preferred that the anionic polymer is an acrylic polymer and the presently most preferred polymers are partly methyl esterified methacrylic acid polymers such as  
25 poly(methacrylic acid, methyl methacrylate) in which the ratio of free acid groups to ester groups is about 1:1 ((e.g. those available from Röhm Pharma GmbH under the Trade Mark EUDRAGIT L), or especially, about 1:2 ((e.g. those available from Röhm Pharma GmbH under the Trade Mark

EUDRAGIT S). In this connection, selection of a particular anionic polymer and the amount thereof can provide the hydrophilic particles with a desired dissolution profile.

5       The amount of anionic polymer used will depend upon the nature and amount of the cation present in the salt, the nature of the impregnating anionic polymer, and the degree of hydrophobicity required. A suitable amount can be determined by simple experimentation but usually the anionic  
10 polymer will be present in an amount of 10 to 50%, preferably 20 to 40, more preferably 25 to 35 and especially about one third, based on the weight of the carbomer complex. Having regard to the small particle size the amount of polymer will be less than the theoretical amount  
15 required to coat the particles, and the swelling and dissolution of the carbomer will not be controlled by pH.

      The polysaccharide particles are impregnated/  
hydrophobised by milling and passing through a suitable  
20 sieve (as aforementioned), stirring the sieved particles into a mixture of e.g. isopropanol and water (solvent) and partly methyl esterified methacrylic acid polymer (e.g. Eudragit S100) at from 20 to 40% by weight of the polysaccharide particles (the solvent/coating solution  
25 having previously been agitated until clear), stirring then evaporating the solvent under vacuum at about 50-70° to leave coated polysaccharide particles. Thereafter the resulting powder can be filled into gelatin capsules ready for enteric coating.

The invention will now be described by way of the following examples.

5 Example 1

Foam Enema Formulation

14,871g of purified water containing 22g of dissolved  
10 methyl paraben and 2g of dissolved propyl paraben as  
preservatives were placed in a 20 litre Moltomat-Universal  
MMU 20 homogenizer. Then 435g of Xanthan gum Keltrol TF  
having a water content of 7.6% (form the Company Kelco) were  
dispersed in the preserved water under efficient  
15 homogenization and reduced pressure.

30g of unbleached lecithin were then added and  
dispersed under homogenization and reduced pressure. At  
this stage the pH of the viscous gel obtained was 6.3. A  
20 solution then made of 0.45 g sodium hydroxide pellets and  
20g of water was added and dispersed under reduced pressure.  
The pH then was 6.93. Finally 155g of Polysorbate 80 (non-  
ionic surfactant) and 4g of Citral (perfume) were added and  
dispersed under reduced pressure.

25

The final foam enema appeared as a slightly hazy gel,  
having a pH of 7.04 and a viscosity of 40'000 mpa.s at 20°C  
as measured using a Brookfield DV II viscometer (1.5 rpm,  
spindle 63).

A foam enema was then produced using this formulation by adding 2.2g of n-butane per 100g of the above formulation in a pressurised mixing unit and the mixture was then filled into bag-in-can aerosol canisters. Each canister contained 23g of the mixture from which 21g of foam was delivered through a valve and an applicator, i.e. about 530 mg of Xanthan gum per delivered dose.

#### 10 Liquid Enema Formulation

To 4,906g of purified water containing 10g of dissolved methyl paraben and 2g of dissolved propyl paraben used as preservatives, 58.95g of Xanthan gum Keltrol TF containing 6.7% water (i.e. 55g dry basis) was added in an homogenizer and dispersed under efficient homogenization under reduced pressure. The pH of the gel obtained was 6.05 and the viscosity was 7,500 mPa.s (22°C - 1.5 rpm-spindle 63 - Brookfield DV II). At this stage 23g of sodium citrate. 2H<sub>2</sub>O was added as buffering agent. The pH went up to 7.15 and the viscosity 40,000 mPa.s measured as above. The formulation, which appears as a slightly hazy gel, was then packed into a bag-in-can canister equipped with a valve and an applicator and pressurised with nitrogen. If the bag of the bag-in-can system is filled with 104g of the formulation above then 100g of the formulation can be delivered through the valve and applicator corresponding to a dose of 1.1g of Xanthan gum.

Example 2

The enema of Example 1 was then given to patients. The patients were twenty adults who had previously undergone  
5 total colectomy with mucosal proctectomy and ileal J-pouch anal anastomosis for ulcerative colitis and who had active chronic pouchitis refractory to standard therapy. Patients had chronic pouchitis, as defined as continuous symptoms of pouchitis for more than 4 weeks and a Pouchitis Disease  
10 Activity Index (PDAI) score of at least 7 points on an 18 point scale. All patients had either failed or were intolerant to metronidazole as well as other commonly used treatments for pouchitis. Mucosal inflammation, determined by endoscopic examination, was limited to the pouch and did  
15 not extend into the ileum proximal to the pouch.

The demographics of the patients entered into the study are presented in Table 1. There were no significant differences in the age, gender distribution, smoking  
20 history, time since the diagnosis of ulcerative colitis, duration of pouch function, time since the first episode of pouchitis, duration of the current episode of pouchitis, or in the medications previously used for treatment of pouchitis. All patients had been on medication for  
25 pouchitis, previously, and one half of the patients were on concurrent treatment for chronic pouchitis (Table 2).

TABLE 1

## PATIENT CHARACTERISTICS

Number of Patients	20
Age (mean)	40 (18-62)
Number of Men:Women	12:8
Number of Cigarette Smokers, current:former:never	1:2:17
Years since diagnosis of Ulcerative colitis. Median (range)	9 (3-32)
Months of pouch function. Median (range)	45 (4-161)
Months since the first episode of pouchitis. Median (range)	42 (3-151)
Months of current pouchitis episode. Median (range)	4 (.8-151)

**TABLE 2****THERAPY FOR POUCHITIS (20 PATIENTS)**

Therapy	No. Of Patients	
	Current	Previous
<b>Antibiotics</b>		
Metronidazole	3	16
Ciprofloxacin	6	15
Amoxicillin/clavulanic acid	1	6
Tetracycline	0	3
Trimethoprine/sulfamethoxazole	1	0
<b>5-ASA</b>		
Sulfasalazine	1	5
Oral mesalamine	0	5
Mesalamine enemas	0	3
Mesalamine suppositories	0	3
<b>Corticosteroids</b>		
Prednisone	1	7
Hydrocortisone enemas	0	5
<b>Immune Modifiers</b>		
Azathioprine	0	0
Cyclosporine	0	0
FK506	0	0
<b>Antidiarrheals</b>		
Loperamide	5	3
Codeine sulfate	0	1

**TABLE 3**

DISEASE ACTIVITY AT BASELINE AND COMPLETION OF TREATMENT  
WITH XANTHAN GUM ENEMA

5

	Baseline Median (range)	Completion Median (range)
Clinical Score	4 (1,5)	3 (0,4) *
Endoscopy Score	5 (1,6)	4 (1,6)
Histology Score	2 (2,6)	2 (2,6)
Total Score (PDAI)	11 (7,16)	9 (2,16) *

\* $p < 0.5$  for within-group change. Baseline vs completion (signed rank test with two missing values at completion filled in by overall (groups) Baseline values).

10

Three patients had to discontinue treatment because of worsening of symptoms, but none developed dehydration or required hospitalization. Three patients had cramping discomfort in the pouch after taking the enema. One of the patients who developed cramps discontinued it because of the discomfort. One patient developed right lower abdominal pain and the study medication was discontinued.

The initial or final endoscopic or histologic scores of the patients are shown in Table 3.

20

In conclusion six of the twenty patients discontinued therapy and nine of fourteen patients (64%) who completed the treatment improved (defined as a reduction in the PDAI score of 3 points or more). This is particularly surprising  
5 in view of the fact that the patients were refractory to conventional therapy.

CLAIMS

1. Use of polysaccharide gum in the preparation of a medicament for the treatment of inflammatory bowel disease.  
5
2. Use as claimed in Claim 1 wherein the disease state is pouchitis.
- 10 3. Use as claimed in Claim 1 wherein the polysaccharide gum is Xanthan gum.
4. Use as claimed in any one of Claims 1 to 3 wherein the medicament is a post-gastric delayed release oral composition or a rectally administrable composition.  
15
5. Use as claimed in Claim 4 wherein the dosage of the polysaccharide per unit dose is 200mg to 2000mg.
- 20 6. Use as claimed in Claim 4 wherein the medicament is an enema or foam enema.
7. A post-gastrically delayed release oral or rectally administrable pharmaceutical composition comprising a polysaccharide gum as the sole therapeutically active agent together with a pharmaceutically acceptable carrier or vehicle.  
25

8. A composition as claimed in Claim 7 which is further defined in accordance with Claims 3 to 6.
9. The use of a polysaccharide gum as the sole therapeutically active agent in the manufacture of a medicament for the treatment or prophylaxis of inflammatory bowel disease.